Hepatectomy Provides Good Long-Term Outcomes for Hepatocellular Carcinoma Patients With Portal Hypertension: A Propensity Score Matching Analysis

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Abstract

**Background:** The role of hepatectomy in hepatocellular carcinoma (HCC) with portal hypertension (PH) remains controversial. This study aimed to evaluate the effect of hepatectomy on overall survival (OS) of HCC patients with PH.

**Methods:** A total of 1651 HCC initially treated with hepatectomy were retrospectively reviewed and divided into PH group (n=157) or non-PH group (n=1494). Propensity score matching (PSM) was conducted to match the baseline characteristics of the PH group and non-PH group.

**Results:** The PH group presented a similar OS \( (p=0.29) \) and recurrence free survival (RFS) \( (p=0.83) \) compared with non-PH group after initial hepatectomy before PSM. After PSM processing, the baseline characteristics were highly comparable for both groups (133 patients in each group). The PH group also presented a similar OS \( (p=0.81) \) and RFS \( (p=0.65) \) compared with non-PH group after initial hepatectomy. After PSM, multivariate analysis identified tumor size (>5 cm) \( (p=0.02) \), macro-venous invasion \( (p < 0.001) \), AST (>37 U/L) \( (p =0.008) \) as independent risk factors for OS.

**Conclusions:** Hepatectomy provides good long-term outcomes for HCC patients with PH. PH should not be regarded as a contraindication for hepatectomy in HCC patients.

Introduction

Primary liver cancer is the second cause of cancer-related death and hepatocellular carcinoma (HCC) accounts for 90% of cases. HCC is common in China because of the high prevalence of hepatitis B virus (HBV) infection and cirrhosis[1]. Previous studies considered hepatectomy as a contraindication for HCC patients with portal hypertension (PH)[2, 3].

Recently, studies showed that HCC patients with PH can benefit from hepatectomy[4–7], while both American Association for the Study of Liver Diseases (AASLD) and the European Association for Study of Liver (EASL) guidelines haven't accepted that opinion[8, 9]. Different diagnosis criteria of PH might result in inconsistent results and increase selection bias. A meta-analysis conducted in 2015 reported that hepatectomy increased the risk of mortality and clinical decompensation for HCC patients with PH (evaluated by any method)[10]. Consequently, liver transplantation and ablation was considered as the first-line treatment for HCC patients with PH[9, 10]. However, only a small amount of HCC patients with PH could receive liver transplantation due to the shortage of liver donor and the expensive cost.

In this study, we retrospectively evaluated the effect of PH on survival of HCC patients initially treated with hepatectomy. Propensity score matching (PSM) was conducted to reduce the heterogeneity between PH patients and non-PH patients and made the results more convincing.

Materials And Methods
Patients

A retrospective study about HCC patients with PH was conducted and was approved by the Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University. The procedures used in the study adhere to the tenets of the Declaration of Helsinki and its later amendments or comparable ethical standards. All enrolled patients should meet the both inclusion criteria: 1) Pathological diagnosis of HCC after hepatectomy, 2) Underwent hepatectomy as initial treatment for HCC. Exclusion criteria were: 1) Underwent trans-arterial chemoembolization (TACE)/ radiofrequency ablation (RFA)/ chemotherapy before hepatectomy, 2) Complicated with other malignant tumors, 3) Patients without follow-up. There were 1651 HCC patients initially treated with hepatectomy enrolled in the study between February 2004 and November 2014.

Most accepted gold diagnosis criteria of PH was hepatic venous pressure gradient (HVPG) over 10 mmHg[10-12]. The presence of gastroesophageal varices (GEV) or platelet count <100,000/mL and splenomegaly (major spleen diameter >12 cm) were considered as standard surrogate criteria to define PH. HVPG was not routinely used in our hospital because of invasiveness. Therefore, in this study PH was defined when one criteria was met: 1) the presence of GEV by CT/MR or endoscopy, 2) platelet count <100,000/mL and splenomegaly (major spleen diameter >12 cm).

There were two groups in the study according to PH criteria: 1) non-PH group: HCC patients without PH before hepatectomy, 2) PH group: HCC patients with PH before hepatectomy. Patients’ clinicopathological variables were collected from our HCC database.

Treatment

Hepatectomy was the initial treatment for HCC and was performed the same as our previous reports[13]. Patients were regularly followed up at outpatient clinics and received liver ultrasound, and serum α-fetoprotein (AFP). Abdominal CT or MRI scan was performed every 6 months or when recurrence was suspected as our previous reports[13]. After initial hepatectomy patients would receive repeated hepatectomy, RFA, TACE, and/or chemotherapy once recurrence was confirmed.

Statistical Analysis

Overall survival (OS) was calculated from the date of hepatectomy to the date of HCC-associated death or the last follow-up, and recurrence free survival (RFS from the date of hepatectomy to the date of recurrence. Student’s t test, Mann-Whitney U test and Chisquare test were used to compare variables. PSM was conducted to match the baseline characteristics of the PH group and non-PH group[14]. The propensity score was calculated based on gender, age, tumor size, tumor number, capsulation, organ invasion, AFP, Edmonson-Steiner stage, HBV infection, micro venous invasion (MVI), macro venous invasion, lymphatic metastasis, cirrhosis, Child-Pugh score, intraoperative bleeding. Subjects were one-to-one matched without replacement with a caliper width of 0.05. The balance of characteristics was measured by their absolute value of standardized differences was < 20%. Survival curves were analyzed
with the Kaplan-Meier method and compared with the log-rank test. Variables with a \( p \) value < 0.10 in univariate analysis were included in a multivariate analysis with Cox proportional-hazards model. All statistical analysis were using R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). A \( p \) value of less than 0.05 was considered statistically significant.

**Result**

**Patients’ Characteristics**

The study totally enrolled 1651 HCC patients initially treated with hepatectomy according to inclusion and exclusion criteria. The baseline characteristics of all enrolled patients were shown in Table 1. There were 1448 male (87.7%) and 203 female (12.3%). There were 157 patients in PH group and 1494 patients in non-PH group. There were 1198 patients (72.6%) developed recurrence and 1009 patients (61.1%) died during follow-up. There were 1545 patients (93.6%) with HBV infection and 989 patients (59.9%) with cirrhosis. The mean tumor size was 8.05 cm, and 542 patients (32.8%) had multiple tumors. According to Edmonson-Steiner stage, there were 42 stage I patients (2.5%), 1123 stage II patients (68.0%), 472 stage III patients (28.6%) and 14 stage IV patients (0.8%). PH group patients had lower level of albumin (ALB) (38.08 vs. 40.16 g/L, \( p < 0.001 \)), alanine aminotransferase (ALT) (48.5 vs. 56.8 U/L, \( p = 0.01 \)), white blood cells (WBC) (4.68 vs. 6.84, \( p < 0.001 \)), tumor size (6.35 vs. 8.23 cm, \( p < 0.001 \)), hemoglobin (HB) (130.9 VS. 137.8 g/L, \( p < 0.001 \)). PH group patients had longer prothrombin time (PT) (13.58 vs. 12.75 s, \( p < 0.001 \)), more intraoperative bleeding (1138.5 vs. 820.7 ml, \( p = 0.05 \)), higher rate of transfusion (72/157, 45.9% vs. 446/1494, 27.1%, \( p < 0.001 \)), higher rate of Child-Pugh classification B (21/157, 13.4% vs. 18/1494, 1.2%, \( p = 0.03 \)). Patients with PH were older than non-PH patients (52.1 vs. 49.6, \( p = 0.003 \)). Both groups had similar rate of HBV infection (\( p = 0.59 \)), similar tumor number (\( p = 0.28 \)), similar capsulation (\( p = 0.55 \)), similar micro/macro venous invasion (\( p = 0.33/0.29 \)), similar Edmonson-Steiner stage (\( p = 0.21 \)).

**Survival Analysis of Total 1651 Patients**

The PH group had a similar OS (\( p = 0.29 \), Fig.1) compared with non-PH group after initial hepatectomy. The 6-month, 1-, 3-, 5-, and 6-year OS rate in non-PH group and PH group were 87.1%, 76.1%, 49.2%, 39.4%, 35.8% and 84.1%, 72.6%, 49%, 34.1%, 31.6%. The PH group had a similar RFS (\( p = 0.83 \), Fig.2) compared with non-PH group after initial hepatectomy. The 6-month, 1-, 2-, 3, and 5-year RFS rate in non-PH group and PH group were 58%, 46.1%, 36.3%, 31.7%, 26.2% and 64.5%, 47%, 35.6%, 32.8%, 24.7%.

**Multivariate Analysis for OS and RFS**

Univariate analysis showed that age, gender, tumor size, multiple, macro venous invasion, MVI, organ invasion, lymphatic metastasis, preoperative AFP, Child-Pugh classification, capsulation, Edmonson-Steiner stage, ALT, aspartate aminotransferase (AST) and intraoperative bleeding were significantly associated with OS. PH was not an independent protective factor for OS (hazard ratio [HR]=0.982, 95% CI 0.792-1.217, \( p = 0.87 \)) by multivariate analysis (Table 2). Tumor size (>5 cm) (\( p < 0.001 \)), tumor number (multiple) (\( p < 0.001 \)), macro venous invasion (\( p < 0.001 \)), MVI (\( p < 0.001 \)), lymphatic metastasis (\( p <
0.001), preoperative AFP (>400 ng/ml) (p=0.005), Child-Pugh classification (B) (p=0.05), non-capsulation (p=0.003), ALT (>40 U/L) (p=0.002), AST (>37 U/L) (p < 0.001), intraoperative bleeding(>400 ml) (p < 0.001) were identified as independent risk factors for OS.

Univariate analysis revealed that age, gender, tumor size, multiple, macro venous invasion, MVI, organ invasion, lymphatic metastasis, preoperative AFP, Child-Pugh classification, capsulation, Edmonson-Steiner stage, ALT, AST and intraoperative bleeding were significantly associated with RFS. PH was not an independent protective factor for RFS (HR=0.923, 95% CI 0.756-1.126, p=0.43) by multivariate analysis (Table 3). Age (>55 years) (p=0.04), gender (female) (p=0.05), tumor size (>5 cm) (p < 0.001), tumor number (multiple) (p < 0.001), macro venous invasion (p < 0.001), MVI (p < 0.001), lymphatic metastasis (p < 0.001), preoperative AFP (>400 ng/ml) (p=0.005), non-capsulation (p=0.004), AST (>37 U/L) (p < 0.001), intraoperative bleeding(>400 ml) (p < 0.001) were independent risk factors for RFS.

**Survival Analysis After PSM Processing**

After PSM processing, the baseline characteristics were highly comparable for both groups (133 patients in each group) (Table 4). The PH group had a similar OS (p=0.81, Fig.3) compared with non-PH group after initial hepatectomy. The 6-month, 1-, 3-, 5-, and 6-year OS rate in non-PH group and PH group were 81.2%, 73.6%, 45.7%, 38.7%, 36% and 84.2%, 71.4%, 48.9%, 35.3%, 32.2%. The PH group had a similar RFS (p=0.65, Fig.4) compared with non-PH group after initial hepatectomy. The 6-month, 1-, 2-, 3, and 5-year RFS rate in non-PH group and PH group were 53.4%, 44.7%, 33.7%, 28.9%, 23.1% and 63.6%, 45.3%, 34.1%, 30.9%, 24%.

**Multivariate Analysis for OS and RFS After PSM Processing**

Tumor size, multiple, macro venous invasion, MVI, organ invasion, lymphatic metastasis, preoperative AFP, capsulation, Edmonson-Steiner stage, ALT, AST and intraoperative bleeding were significantly associated with OS by univariate analysis. While multivariate analysis identified tumor size (>5 cm) (p=0.02), macro venous invasion (p < 0.001), AST (>37 U/L) (p =0.008) as independent risk factors for OS. Organ invasion and lymphatic metastasis presented as marginally significant with OS (multivariate analysis: p= 0.07, p= 0.08).

Tumor size, multiple, macro venous invasion, MVI, organ invasion, lymphatic metastasis, preoperative AFP, Child-Pugh classification, capsulation, Edmonson-Steiner stage, ALT, AST and intraoperative bleeding were significantly associated with RFS by univariate analysis. Multivariate analysis identified tumor size (>5 cm) (p=0.04), macro venous invasion (p < 0.001), lymphatic metastasis (p= 0.001) as independent risk factors for RFS. Organ invasion presented as marginally significant with RFS (multivariate analysis: p= 0.06).Importantly, multivariate analysis presented that PH were not an independent risk factor for OS (HR=1.061, 95% CI 0.771-1.46, p=0.71) and RFS (HR=0.986, 95% CI 0.736-1.322, p=0.93).

**Discussion**
We conducted a large retrospective study based on 1651 HCC patients with sufficient follow-up data to determine the effect of PH on prognosis of HCC patients initially treated with hepatectomy. And our results demonstrated that PH was not an independent risk factor for OS and RFS. This is the largest sample size to evaluate the effect of PH on the OS and RFS of HCC patients initially treated with hepatectomy as we knew.

According to the treatment guidelines of BCLC staging system\cite{15}, 2001 EASL\cite{16}, 2011 AASLD\cite{8}, and 2012 EASL-EORTC\cite{9}, PH was a contraindication for hepatectomy. Two studies in 1996 and 1999 by Barcelona group concluded that PH was a risk factor of postoperative liver decompensation and poor OS after hepatectomy\cite{2,3}. In these two studies, PH was defined as HPVG \( \geq \) 10 mmHg.

Sae Byeol Choi et al. conducted a meta-analysis included 11 observational studies and showed that PH group had higher rates of postoperative complications and poorer survival compared with non-PH group for HCC patients after hepatectomy\cite{17}. Annalisa Berzigotti et al. conducted a meta-analysis in 2015 showed that PH was a risk factor of higher mortality and postoperative clinical decompensation after hepatectomy for HCC\cite{10}. Berzigotti et al. proposed that the presence of PH should be investigated before surgery and HVPG should be used in HCC patients to diagnose PH excepted those patients who have GEV. Liu et al. conducted a meta-analysis and concluded that PH had a negative impact on prognoses of HCC patients underwent hepatectomy\cite{18}. However, Liu et al. also found that PH was not a risk factor for OS of a subgroup of European HCC patients underwent hepatectomy whose PH was diagnosed by the standard surrogate criteria. E. Boleslawski et al. included 40 HCC patients and concluded that an increased HVPG was associated with postoperative liver dysfunction and mortality after hepatectomy\cite{11}.

However, a consensus report from the 5th Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE 2014), all (10/10) experts hold that PH was not an absolute contraindication for hepatectomy of HCC\cite{19}. Takao Ohkudo et al. reported that PH was not associated with the OS and morbidity rate of HCC patients treated with hepatectomy thus HCC patients with PH could be candidates for hepatectomy\cite{6}. Chetana Lim et al. showed that laparoscopic hepatectomy is safe in BCLC 0-A patients with PH and called for re-evaluation of the BCLC guidelines\cite{20}. However, Chetana Lim's research only included 45 HCC patients, the small sample size could not get a convincing result.

Liver transplantation is the best curative treatment for HCC patients with cirrhosis\cite{15}. However, grafts shortages, high medical costs and long waiting period are severe problems worldwide. A research of 243 HCC patients with cirrhosis listed for liver transplantation found that PH was associated with dropout owing to tumor progression\cite{21}. Alternative treatment strategies for HCC patients with PH are needed. Dai et al. reported that the 1-, 3-, and 5-year RFS and OS rate of HCC patients with PH received hepatectomy and liver transplantation were similar\cite{22}. Hepatectomy should be regarded as the first line treatment option for early HCC patients with PH\cite{22}. Fang et al. retrospectively enrolled 280 early-stage HCC patients and found that PH was not associated with poor outcomes after RFA. Qiu et al. conducted a
PSM study and proved that hepatectomy was safe and had a survival advantage over ablation in HCC patients[23].

For HCC patients with cirrhosis who underwent TACE, Nam Hee Kim et al. found that PH was a major negative factor[24]. However, Xiao et al. found that hepatectomy provided better long-term prognosis for HCC patients with PH than TACE and ablation[25]. N. Takemura et al. found that perioperative prophylactic management could enhance the safety of hepatectomy and expanded the indications of hepatectomy in patients with PH[26]. These reports strongly suggest that PH is not an absolute contraindication for hepatectomy of HCC patients and hepatectomy should be considered as first line treatment option for HCC patients with PH in selected cases.

HVPG was not routinely performed in our hospital since its invasiveness. In this retrospective study, GEV or platelet count < 100,000/mL and splenomegaly were used to diagnose PH. Research showed that the association between PH and clinical outcome was greater when HVPG was applied to diagnose PH[10]. HVPG could directly diagnose even small increases of portal pressure[27, 28]. GEV was related to PH since study shown that GEV only form when HVPG was over 10 mmHg. However, platelet count < 100,000/mL and splenomegaly are not accurate enough to diagnose PH. These results strongly suggest that HVPG should be as gold diagnosis criteria of PH. Recently a non-invasive Computed Tomography based assessment was proposed and shown a high accuracy in diagnose of PH and could replace the HVPG assessment[29]. Liver stiffness assessed by transient elastography may be another choice to diagnose PH[30].

There are some limitations in our study. First, this is a single center study and need multiple-centers studies to validate our results. Second, as a retrospective study patients with no follow-up data were excluded in our study and these patients may influenced the results. Third, we use standard surrogate criteria to diagnose PH and may cause selection bias since HVPG is gold diagnose criteria.

In conclusion, hepatectomy provides good long-term outcomes for HCC patients with PH. Our results suggest that PH should not be regarded as a contraindication for hepatectomy of HCC patients.

List Of Abbreviations

- AFP: α-fetoprotein
- ALT: alanine aminotransferase
- ALB: albumin
- AASLD: American Association for the Study of Liver Diseases
- AST: aspartate aminotransferase
- EASL: European Association for Study of Liver
- GEV: gastroesophageal varices
- HB: hemoglobin
- HBV: hepatitis B virus
- HVPG: hepatic venous pressure gradient
- HCC: hepatocellular carcinoma
- MVI: micro venous invasion
- OS: overall survival
- PH: portal hypertension
- PSM: propensity score matching
- PT: prothrombin time
- RFA: radiofrequency ablation
- RFS: recurrence free survival
- TACE: trans-arterial chemoembolization
- WBC: white blood cells

Declarations
Ethics approval and consent to participate: This research was approved by the Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University. The procedures used in the study adhere to the tenets of the Declaration of Helsinki and its later amendments or comparable ethical standards. All patients included in the study had received informed consent.

Consent for publication: Consent for publication had been obtained from all HCC patients.

Availability of data and materials: The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: Xiwen Wu, Wei Chen have equally contributed to this article as first authors. Baogang Peng and Shunli Shen have equally contributed to this article as last and corresponding authors. Baogang Peng and Shunli Shen conceived and designed the study. Xiwen Wu, Wei Chen, Bin Chen, Wenxuan Xie and Shutong Wang collected and analyzed the data. Xiwen Wu, Wei Chen, Baogang Peng and Shunli Shen interpreted the data. Xiwen Wu, Wei Chen, Baogang Peng and Shunli Shen drafted or wrote the manuscript.

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Tables
Table 1
Baseline clinical and intraoperative characteristics of total patients before PSM.

| Variable                        | Before PSM                      | non-PH (n = 1494) | PH (n = 157) | p     |
|---------------------------------|---------------------------------|-------------------|--------------|-------|
|                                 | Total (n = 1651)                |                   |              |       |
| Age                             | 49.81 ± 12.19                   | 49.57 ± 12.37     | 52.10 ± 10.03| 0.003 |
| Gender (male: female)           | 1448:203                       | 1309:185          | 139:18       | 0.84  |
| HBV (yes: no)                   | 1545:106                       | 1396:98           | 149:8        | 0.59  |
| ALT (U/L)                       | 56.04 ± 64.76                  | 56.84 ± 67.01     | 48.51 ± 36.25| 0.01  |
| AST (U/L)                       | 60.16 ± 59.11                  | 59.99 ± 59.62     | 61.76 ± 54.12| 0.70  |
| ALB (g/L)                       | 39.97 ± 4.60                   | 40.16 ± 4.51      | 38.08 ± 5.06 | <0.001|
| TB (µmol/L)                     | 20.71 ± 38.41                  | 20.88 ± 40.24     | 19.09 ± 10.11| 0.17  |
| WBC (10⁹/L)                     | 6.63 ± 2.43                    | 6.84 ± 2.35       | 4.68 ± 2.33  | <0.001|
| HB (g/L)                        | 137.16 ± 20.55                 | 137.82 ± 20.46    | 130.92 ± 20.45| <0.001|
| PT (s)                          | 12.83 ± 1.32                   | 12.75 ± 1.29      | 13.58 ± 1.30 | <0.001|
| Ascites (ml)                    | 37.95 ± 217.16                 | 35.22 ± 208.84    | 63.89 ± 283.98| 0.22  |
| Tumor size (cm)                 | 8.05 ± 4.45                    | 8.23 ± 4.45       | 6.35 ± 4.13  | <0.001|
| Tumor number (1:2:3:3)          | 1109:351:75:116                | 994:327:68:105    | 115:24:7:11  | 0.28  |
| Multiple (no: yes)              | 1109:542                       | 994:500           | 115:42       | 0.11  |
| Preoperative AFP (ng/l)         | 296.05 [18.43,6278.63]          | 334.26 [17.84,6778.27] | 103.69 [19.00,2746.95] | 0.07  |
| Bleeding (ml)                   | 850.91 ± 1459.85               | 820.69 ± 1396.39  | 1138.54 ± 1946.18 | 0.05  |
| Transfusion (no: yes)           | 1133:518                       | 1048:446          | 85:72        | <0.001|
| Capsulation (intact: deficiency: no) | 1222:418:11       | 1109:376:9       | 113:42:2     | 0.55  |
| Organ invasion (no: yes)        | 1560:91                        | 1412:82           | 148:9        | 1     |
| Macro venous invasion (no: yes) | 1290:361                       | 1173:321          | 117:40       | 0.29  |
| BCLC (0:A:B:C)                  | 40:866:358:387                 | 26:787:336:345    | 14:79:22:42  | <0.001|

Abbreviations: PH portal hypertension, PSM Propensity score matching, AFP α-fetoprotein; WBC white blood cell, HGB hemoglobin, PLT platelets, ALT alanine aminotransferase, AST aspartate transaminase, ALB serum albumin, TB total bilirubin, PT prothrombin time, HBV hepatitis B virus, BCLC Barcelona Clinic Liver Cancer staging system.
| Variable                                | Before PSM |        |        | p  |
|-----------------------------------------|------------|--------|--------|----|
|                                         | Total (n = 1651) | non-PH (n = 1494) | PH (n = 157) |    |
| Lymphatic metastasis (no: yes)          | 1618:33    | 1464:30 | 154:3  | 1  |
| Micro venous invasion (no: yes)         | 1415:236   | 1285:209 | 130:27 | 0.33 |
| Edmonson stage (Ⅰ: Ⅱ: Ⅲ: Ⅳ)           | 42:1123:472:14 | 37:1007:436:14 | 5:116:36:0 | 0.21 |
| Child-Pugh classification (A:B)         | 1512:139   | 1376:118 | 136:21 | 0.03 |

Abbreviations: PH portal hypertension, PSM Propensity score matching, AFP α-fetoprotein; WBC white blood cell, HGB hemoglobin, PLT platelets, ALT alanine aminotransferase, AST aspartate transaminase, ALB serum albumin, TB total bilirubin, PT prothrombin time, HBV hepatitis B virus, BCLC Barcelona Clinic Liver Cancer staging system.
Table 2
Uni-multivariate analysis for OS of Total patients

| Variables                                        | Univariate analysis | Multivariate analysis |
|--------------------------------------------------|---------------------|-----------------------|
|                                                  | $p$ | HR | 95%CI       | $p$ |
| Age>55(yes: no)                                  | 0.004 | 0.889 | 0.779–1.014 | 0.08 |
| Gender(female: male)                             | 0.007 | 0.904 | 0.732–1.115 | 0.35 |
| Tumor size(>5:<5)                                | <0.001 | 1.403 | 1.178–1.67 | <0.001 |
| Multiple(yes: no)                                | <0.001 | 1.406 | 1.234–1.603 | <0.001 |
| Macro venous invasion(yes: no)                   | <0.001 | 1.623 | 1.395–1.889 | <0.001 |
| Micro venous invasion(yes: no)                   | <0.001 | 1.512 | 1.278–1.79 | <0.001 |
| Organ invasion(yes: no)                          | <0.001 | 1.143 | 0.894–1.461 | 0.29 |
| Lymphatic metastasis(yes: no)                    | <0.001 | 2.446 | 1.682–3.555 | <0.001 |
| Preoperative AFP(>400:<400)                       | <0.001 | 1.208 | 1.06–1.377 | 0.005 |
| Child-Pugh classification(B:A)                   | <0.001 | 1.233 | 1.004–1.516 | 0.05 |
| Portal Hypertension(yes: no)                     | 0.29  | 0.982 | 0.792–1.217 | 0.87 |
| Capsulation intact(no: yes)                      | <0.001 | 1.245 | 1.079–1.437 | 0.003 |
| Edmonson stage(Ⅰ+:Ⅱ+Ⅲ:IV)                       | <0.001 | 1.001 | 0.886–1.13 | 0.99 |
| Cirrhosis(yes: no)                               | 0.42  | 1.058 | 0.924–1.211 | 0.41 |
| HBV(yes: no)                                     | 0.33  |       |             |     |
| ALT(>40:<40)                                     | <0.001 | 0.792 | 0.683–0.918 | 0.002 |
| AST(>37:<37)                                     | <0.001 | 1.654 | 1.408–1.944 | <0.001 |
| Bleeding ≥ 400 ml(yes: no)                       | <0.001 | 1.558 | 1.356–1.791 | <0.001 |

Abbreviations: AFP α-fetoprotein; ALT alanine aminotransferase, AST aspartate transaminase, HBV hepatitis B virus.
# Table 3
Uni-multivariate analysis for RFS of Total patients

| Variables                              | Univariate analysis | Multivariate analysis |
|----------------------------------------|---------------------|-----------------------|
|                                        | p       | HR  | 95% CI    | p      |
| Age ≥ 55 (yes: no)                      | <0.001  | 0.882 | 0.782–0.996 | 0.04   |
| Gender (female: male)                   | <0.001  | 0.758 | 0.627–0.917 | 0.004  |
| Tumor size ≤ 5 ≤ 50                    | <0.001  | 1.305 | 1.124–1.515 | <0.001 |
| Multiple (yes: no)                      | <0.001  | 1.38  | 1.221–1.558 | <0.001 |
| Macro venous invasion (yes: no)         | <0.001  | 1.609 | 1.396–1.855 | <0.001 |
| Micro venous invasion (yes: no)         | <0.001  | 1.454 | 1.239–1.707 | <0.001 |
| Organ invasion (yes: no)                | <0.001  | 1.163 | 0.919–1.471 | 0.21   |
| Lymphatic metastasis (yes: no)          | <0.001  | 2.142 | 1.46–3.143  | <0.001 |
| Preoperative AFP ≤ 400 ≤ 400            | <0.001  | 1.297 | 1.15–1.462  | <0.001 |
| Child-Pugh classification (B: A)        | <0.001  | 1.14  | 0.929–1.399 | 0.21   |
| Portal Hypertension (yes: no)           | 0.83    | 0.923 | 0.756–1.126 | 0.43   |
| Capsulation intact (no: yes)            | <0.001  | 1.214 | 1.063–1.388 | 0.004  |
| Edmonson stage (+: +): (–: –)            | <0.001  | 1.049 | 0.939–1.172 | 0.39   |
| Cirrhosis (yes: no)                     | 0.21    |      |            |        |
| HBV (yes: no)                           | 0.35    |      |            |        |
| ALT ≤ 40 ≤ 40                           | <0.001  | 0.895 | 0.779–1.029 | 0.12   |
| AST ≤ 37 ≤ 37                           | <0.001  | 1.412 | 1.216–1.64  | <0.001 |
| Bleeding ≥ 400 ml (yes: no)             | <0.001  | 1.251 | 1.103–1.418 | <0.001 |

Abbreviations: AFP α-fetoprotein; ALT alanine aminotransferase, AST aspartate transaminase, HBV hepatitis B virus.
| Variable                        | After PSM                      |
|--------------------------------|--------------------------------|
|                                | Total (n = 266) | non-PH(n = 133) | PH(n = 133) | p      |
| Age                            | 51.85 ± 11.04   | 51.89 ± 11.68   | 51.80 ± 10.41 | 0.95   |
| Gender(male: female)           | 241:25          | 121:12          | 120:13      | 1      |
| HBV(yes: no)                   | 255:11          | 129:4           | 126:7       | 0.54   |
| ALT(U/L)                       | 53.69 ± 50.14   | 57.38 ± 60.28   | 50.00 ± 37.22 | 0.23   |
| AST(U/L)                       | 59.43 ± 54.22   | 56.71 ± 52.18   | 62.14 ± 56.25 | 0.41   |
| ALB(g/L)                       | 38.87 ± 4.99    | 39.34 ± 5.00    | 38.41 ± 4.94 | 0.13   |
| TB(µmol/L)                     | 22.07 ± 46.51   | 25.70 ± 65.08   | 18.43 ± 8.96 | 0.2    |
| WBC(10⁹/L)                     | 5.81 ± 2.75     | 6.76 ± 2.77     | 4.85 ± 2.38  | <0.001 |
| HB(g/L)                        | 135.19 ± 21.47  | 139.01 ± 20.95  | 131.38 ± 21.38 | 0.004  |
| PT(s)                          | 13.18 ± 1.20    | 12.84 ± 1.19    | 13.52 ± 1.11 | <0.001 |
| Ascites(ml)                    | 55.83 ± 252.63  | 42.26 ± 183.46  | 69.40 ± 306.75 | 0.38   |
| Tumor size(cm)                 | 6.82 ± 4.00     | 6.85 ± 3.70     | 6.78 ± 4.29  | 0.89   |
| Tumor number(1:2:3:3)          | 180:52:17:17    | 88:29:10:6      | 92:23:7:11  | 0.43   |
| Multiple(no: yes)              | 180:86          | 88:45           | 92:41       | 0.69   |
| Preoperative AFP(ng/l)         | 119.84 [19.00,4133.14] | 120.13 [19.00,4589.00] | 119.55 [19.00,4031.67] | 0.91   |
| Bleeding(ml)                   | 953.38 ± 1574.23 | 792.86 ± 908.00 | 1113.91 ± 2024.54 | 0.1    |
| Transfusion(no: yes)           | 164:102         | 86:47           | 78:55       | 0.38   |
| Capsulation(intact: deficiency: no) | 199:65:2     | 104:29:0        | 95:36:2     | 0.21   |
| Organ invasion(no: yes)        | 250:16          | 123:10          | 127:6       | 0.44   |
| Macro venous invasion(no: yes) | 199:67          | 99:34           | 100:33      | 1      |
| BCLC(0:A:B:C)                  | 12:132:51:71    | 3:64:29:37      | 9:68:22:34  | 0.24   |

Abbreviations: PH portal hypertension, PSM Propensity score matching, AFP α-fetoprotein; WBC white blood cell, HGB hemoglobin, PLT platelets, ALT alanine aminotransferase, AST aspartate transaminase, ALB serum albumin, TB total bilirubin, PT prothrombin time, HBV hepatitis B virus, BCLC Barcelona Clinic Liver Cancer staging system.
| Variable                               | After PSM                      |
|----------------------------------------|--------------------------------|
|                                        | Total (n = 266)               |
|                                        | non-PH(n = 133)               |
|                                        | PH(n = 133)                   |
|                                        | p                             |
| Lymphatic metastasis(no: yes)          | 259:7                         |
|                                        | 128:5                         |
|                                        | 131:2                         |
|                                        | 0.44                          |
| Micro venous invasion(no: yes)         | 225:41                        |
|                                        | 116:17                        |
|                                        | 109:24                        |
|                                        | 0.31                          |
| Edmonson stage(1:2:3:4)                | 11:186:68:1                  |
|                                        | 7:93:32:1                     |
|                                        | 4:93:36:0                     |
|                                        | 0.56                          |
| Child-Pugh classification(A:B)         | 236:30                        |
|                                        | 117:16                        |
|                                        | 119:14                        |
|                                        | 0.85                          |

Abbreviations: PH portal hypertension, PSM Propensity score matching, AFP α-fetoprotein; WBC white blood cell, HGB hemoglobin, PLT platelets, ALT alanine aminotransferase, AST aspartate transaminase, ALB serum albumin, TB total bilirubin, PT prothrombin time, HBV hepatitis B virus, BCLC Barcelona Clinic Liver Cancer staging system.
| Variables                                | Univariate analysis | Multivariate analysis |
|------------------------------------------|---------------------|-----------------------|
|                                          | p       | HR       | 95%CI   | p      |
| Age (55: yes: no)                        | 0.71    | 0.913    | 0.665–1.254 | 0.57  |
| Gender (female: male)                    | 0.76    | 1.293    | 0.725–2.305 | 0.38  |
| Tumor size (<5: ≤5)                     | <0.001 | 1.611    | 1.091–2.377 | 0.02  |
| Multiple (yes: no)                       | <0.001 | 1.196    | 0.857–1.67  | 0.29  |
| Macro venous invasion (yes: no)          | <0.001 | 1.972    | 1.342–2.897 | <0.001|
| Micro venous invasion (yes: no)          | 0.002   | 1.349    | 0.885–2.054 | 0.16  |
| Organ invasion (yes: no)                 | <0.001 | 1.691    | 0.952–3.004 | 0.07  |
| Lymphatic metastasis (yes: no)           | 0.004   | 2.075    | 0.923–4.668 | 0.08  |
| Preoperative AFP (≤400: <400)            | 0.008   | 0.925    | 0.647–1.322 | 0.67  |
| Child-Pugh classification (B: A)         | 0.1     | 1.123    | 0.704–1.791 | 0.63  |
| Portal Hypertension (yes: no)            | 0.81    | 1.061    | 0.771–1.46  | 0.71  |
| Capsulation intact (no: yes)             | 0.03    | 0.84     | 0.568–1.243 | 0.38  |
| Edmonson stage (+: +: +)                  | <0.001 | 1.275    | 0.934–1.74  | 0.13  |
| HBV (yes: no)                            | 0.48    |          |         |       |
| ALT (≥40: ≤40)                           | 0.03    | 0.961    | 0.661–1.398 | 0.83  |
| AST (≥37: ≤37)                           | <0.001 | 1.75     | 1.16–2.64   | 0.008 |
| Bleeding ≥ 400 ml (yes: no)              | <0.001 | 1.249    | 0.879–1.773 | 0.22  |

Abbreviations: AFP α-fetoprotein; ALT alanine aminotransferase, AST aspartate transaminase, HBV hepatitis B virus.
Table 6
Uni-multivariate analysis for RFS of patients after PSM

| Variables                  | Univariate analysis | Multivariate analysis |
|----------------------------|---------------------|-----------------------|
|                            | $p$                 | HR  | 95% CI       | $p$ |
| Age $>55$ (yes: no)        | 0.32                | 0.85 | 0.632–1.144 | 0.28 |
| Gender (female: male)      | 0.42                | 1.051 | 0.611–1.805 | 0.86 |
| Tumor size (≤5: <5)        | <0.001              | 1.426 | 1.011–2.012 | 0.04 |
| Multiple (yes: no)         | 0.004               | 1    | 0.721–1.386 | 1    |
| Macro venous invasion (yes: no) | <0.001            | 2.37  | 1.652–3.4   | <0.001 |
| Micro venous invasion (yes: no) | <0.001         | 1.299 | 0.861–1.96  | 0.21 |
| Organ invasion (yes: no)   | 0.003               | 1.747 | 0.987–3.092 | 0.06 |
| Lymphatic metastasis (yes: no) | <0.001         | 4.205 | 1.77–9.987 | 0.001 |
| Preoperative AFP (≤400: <400) | 0.02            | 0.935 | 0.669–1.307 | 0.69 |
| Child-Pugh classification(B:A) | 0.04              | 1.175 | 0.749–1.844 | 0.48 |
| Portal Hypertension (yes: no) | 0.65            | 0.986 | 0.736–1.322 | 0.93 |
| Capsulation intact (no: yes) | 0.04             | 0.868 | 0.61–1.254  | 0.45 |
| Edmonson stage (+: +: +)   | <0.001             | 1.287 | 0.953–1.737 | 0.1  |
| HBV (yes: no)              | 0.82                |      |              |     |
| ALT (≤40: <40)             | 0.006               | 1.21  | 0.844–1.734 | 0.3  |
| AST (≤37: <37)             | <0.001              | 1.121 | 0.766–1.64  | 0.56 |
| Bleeding ≥ 400 ml (yes: no) | 0.004            | 1.044 | 0.752–1.449 | 0.8  |

Abbreviations: AFP α-fetoprotein; ALT alanine aminotransferase, AST aspartate transaminase, HBV hepatitis B virus.