

Original Article

Timing of spontaneous hepatocellular carcinoma rupture as a prognostic indicator

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Abstract: The prognostic value of spontaneous ruptured hepatocellular carcinoma (rHCC) and its interaction with Barcelona Clinic Liver Cancer (BCLC) stages remain unclear. To assess the prognostic effects of rHCC and its interaction with BCLC staging. This was a retrospective cohort study enrolled 2,577 patients with hepatocellular carcinoma. rHCC was diagnosed using computed tomographic evidence of capsular disruption with extravasation of blood and classified as early or late according to whether rupture occurred ≤ 7 days or > 7 days after HCC diagnosis, respectively. Propensity score matching (PSM) was used to adjust for confounders. Cox proportional hazards regression models and Kaplan-Meier survival analyses were used to assess the prognostic effects of rHCC across BCLC stages. Of 2,577 patients, 102 (4.0%) had rHCC. Patients with rHCC were younger and had higher BCLC stages, worse liver function, and higher α -fetoprotein levels than those without rHCC. Multivariable Cox regression analysis revealed that late rHCC was a predictor of worse overall survival (OS; hazard ratio [HR]: 1.578, 95% confidence interval [CI]: 1.059-2.351) and that early rHCC was a protective factor (HR: 0.717, 95% CI: 0.519-0.992). A combination of early and late rupture did not predict OS. Kaplan-Meier analysis after PSM revealed that the OS for patients with early rHCC at BCLC stage B or C was similar to that for patients without rHCC ($P = .594$ for stage B and $P = .566$ for stage C) and that OS for patients with late rHCC at BCLC stage B or C was significantly worse than that for patients without rHCC ($P = .007$ for stage B and $P = .006$ for stage C). Late rHCC is associated with worse outcomes than early rHCC or nonruptured HCC at BCLC stages B and C.

Keywords: Barcelona clinic liver cancer stage, early or late rupture, overall survival, propensity score matching, ruptured hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related mortality globally, with an estimated 815,000 new cases and 750,000 deaths annually [1]. HCC disproportionately affects regions where hepatitis B virus (HBV) and hepatitis C virus (HCV) are endemic, such as East Asia, Southeast Asia, and North Africa [2, 3]. Spontaneous ruptured HCC (rHCC) is a life-threatening complication that occurs in

2.3%-26% of patients with HCC [4, 5]. rHCC is characterized by tumor capsule disruption and intraperitoneal hemorrhage. Diagnosing spontaneous rHCC is difficult, especially in patients without a history of HCC [6, 7]. Timely surgical intervention is crucial. Patients who receive only supportive care are unlikely to survive rHCC, which has a mortality rate of 85%-100%. By contrast, among patients with rHCC who receive timely surgical intervention, the mortality rate is 23.5% [5]. Patients may also undergo transarterial embolization (TAE), which is an

effective method that controls bleeding (success rate, 53%-100%) [4] and poses a lower risk of complications than does emergency surgery [8]. Surgical intervention and TAE both yield superior outcomes than supportive care [9], highlighting the need for tailored therapeutic strategies based on tumor stage and liver function.

The Barcelona Clinic Liver Cancer (BCLC) staging system, the gold standard for prognostic stratification and treatment allocation in HCC, accounts for tumor burden, hepatic reserve, and performance status as a guide to management [10]. The prognostic implications of rHCC in the context of the BCLC framework remain undefined; the BCLC staging system lacks explicit recommendations for this complication [11]. Several studies have suggested that rHCC may necessitate stage migration because of its association with worse survival. Nevertheless, large-scale and well-controlled studies on this topic are lacking [12-15].

This study investigated the prognostic effects of rHCC and its interaction with BCLC staging to refine risk stratification and guide therapeutic decision-making.

Material and methods

Patients

This retrospective cohort study enrolled 2,577 adult patients (> 18 years) with HCC treated at China Medical University Hospital (CMUH) between January 2012 and February 2022. HCC diagnosis was made according to European Association for the Study of the Liver (EASL) guidelines and based on pathological findings or typical radiological presentations from at least two imaging investigations, including hepatic arterial angiography, contrast-enhanced dynamic computed tomography (CT), and magnetic resonance imaging [16]. HCC stage was classified in accordance with the BCLC staging system [10, 17]. Spontaneous rHCC was defined as capsular disruption with contrast extravasation or perihepatic hemoperitoneum (≥ 40 Hounsfield units) as observed using dynamic CT. This was supplemented by clinical signs of acute abdomen (i.e., sudden pain with hemodynamic instability or peritoneal sign) or the presence of hemorrhagic ascites (red blood cell count > 50,000/ μ L in paracentesis fluid). Cases with traumatic etiology or indeterminate imaging were excluded [7].

We consecutively enrolled patients regardless of treatment status. Patients were excluded if they had concurrent extrahepatic malignancies or had received liver transplantation as the initial treatment. Using structured electronic medical records, we collected data on demographic characteristics, tumor characteristics (i.e., BCLC stage, tumor number, maximum tumoral diameter in CT findings, and radiologically confirmed vascular invasion [18]), baseline laboratory parameters, and initial treatment strategies.

To evaluate the effect of rHCC on prognosis, we analyzed baseline demographics and tumor characteristics. We analyzed age, sex, HCC etiology (HBV, HCV, or alcohol consumption), tumor size (> 5 cm vs. ≤ 5 cm) [10], tumor count (single or multiple), portal vein tumor thrombosis (PVTT), liver reserve (Child-Pugh classification; class B or C defined as poor hepatic reserve), and serum α -fetoprotein levels (AFP).

This study was conducted in accordance with the principles of the Declaration of Helsinki (1975, revised in 2013) and received approval from the Institutional Review Board of CMUH, Taichung, Taiwan (CMUH108-REC3-140). Patient identification numbers were encrypted to ensure privacy. The need for informed consent was waived.

Laboratory tests and HCC etiologies

Complete blood counts (Sysmex, Kanagawa, Japan) and blood biochemistry data (Beckman Coulter, Brea, CA, USA) were analyzed at the hospital's central laboratory. HBV infection was defined as the presence of hepatitis B surface antigen (HBsAg). HCV infection was defined as the presence of HCV antibodies and detectable HCV RNA. Male and female participants who consumed > 30 and > 20 g of alcohol per day (or > 210 and > 140 g of alcohol per week), respectively, were considered to have consumed alcohol [19]. PVTT was defined as portal vein invasion above the segmental or second-order branches of the portal vein, detected using imaging or by pathological evidence of macrovascular invasion [20].

Onset of rHCC

To investigate the prognostic impact of the timing of spontaneous HCC rupture, we defined

early rupture and late rupture according to the interval between HCC diagnosis and the onset of rupture. As our institution is a referral center, patients with rHCC may be initially diagnosed at other hospitals and subsequently transferred to our center. Therefore, a 7-day interval was used to account for the potential delay between initial presentation, diagnosis, and referral. HCC diagnosed at the time of rupture or ruptured soon after HCC diagnosis without treatment was defined as early rupture (≤ 7 days after HCC diagnosis), and the median interval between the onset of symptoms and diagnosis was 0 (0-1) day. Tumor rupture that occurred subsequent to HCC treatment (> 7 days after HCC diagnosis) was defined as late rupture, and the median interval between HCC diagnosis and onset of HCC rupture was 56 (20-121) days.

Treatment of HCC

The Liver Cancer Clinical Practice Guidelines of CMUH were established in accordance with the clinical practice guidelines of the American Association for the Study of Liver Diseases and the EASL [16, 21]. At CMUH, indications for and the extent of radiofrequency ablation (RFA) required (alone or in combination with percutaneous ethanol injection) are determined by experienced hepatologists and surgeons in accordance with institutional protocols described elsewhere [22, 23]. Likewise, criteria for surgical resection are determined in accordance with established protocols. Transarterial chemoembolization (TACE) is considered for patients with preserved liver function (Child-Pugh score ≤ 8) and either a patent portal vein or portal vein thrombosis accompanied by collateral circulation. Detailed methodologies for TACE and radiotherapy have been published elsewhere [24, 25]. Systemic therapies include tyrosine kinase inhibitors, immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab, and atezolizumab plus bevacizumab), and cytotoxic chemotherapy using carboplatin-based or gemcitabine-based regimens. All systemic treatments are administered in accordance with current guidelines and dosing protocols [26].

Statistical analyses

Baseline characteristics are reported as median (interquartile range) for continuous variables or frequency (percentage) for categorical vari-

ables. Groups were compared using the Mann-Whitney U test for continuous variables and the Pearson chi-square test for categorical variables. Multivariable logistic regression was conducted with adjustments for confounders and risk factors for rHCC. Overall survival (OS) was defined as the time from the date of HCC diagnosis to death from any cause, and data were censored at death, loss, or the end of the follow-up period (February 28, 2022). Cox proportional hazards regression models and Kaplan-Meier survival analyses were used to assess the prognostic effects of rHCC across BCLC stages.

We adjusted for confounders by performing propensity score matching (PSM). This allowed us to conduct stratified survival analyses and isolate the prognostic effects of rHCC. Nearest-neighbor matching (1:4 ratio) was applied, with $P > .05$ indicating balance. Kaplan-Meier analyses were conducted before and after PSM. Subgroup analyses were performed to identify associations of various characteristics with survival rates.

All analyses were performed in IBM SPSS Statistics 25 (SPSS, Chicago, IL), with $P < .05$ considered statistically significant.

Results

Baseline characteristics

Between January 1, 2012, and February 28, 2022, 2,729 patients with HCC were treated at CMUH. After excluding patients with mixed HCC or other malignancies ($n = 12$) and patients who underwent liver transplantation as the first-line treatment ($n = 140$), we enrolled 2,577 patients (**Figure 1**). Of the enrolled patients, 102 (4.0%) had rHCC. Among the patients with rHCC, 71 (69.6%) and 31 (30.4%) had early and late rHCC, respectively. Patients with rHCC were younger (median age: 60.0 years vs. 65.0 years), were more likely to have intermediate to advanced cancer (BCLC stages C or D: 66.7% vs. 31.4%), were more likely to have poor hepatic reserve (Child-Pugh class B or C: 60.8% vs. 21.6%), and had higher AFP levels compared with those without rHCC (**Table 1**).

Factors associated with rHCC

Results from a univariate logistic regression analysis indicated that younger age, HCV infec-

Timing of spontaneous HCC rupture

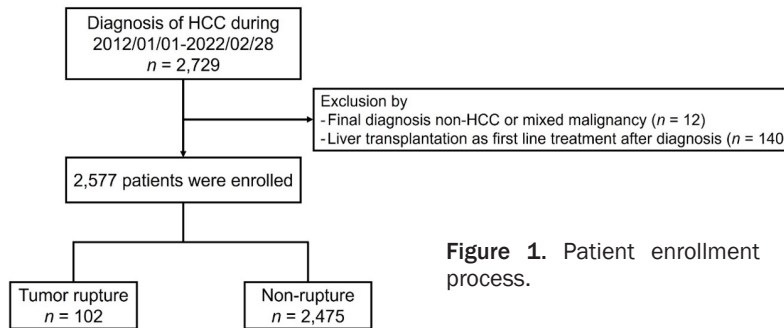


Figure 1. Patient enrollment process.

tion, poor hepatic reserve, AFP > 400 ng/mL, maximal tumor size > 5 cm, PVTT, and multiple tumors were risk factors for rHCC. In the multivariable analysis, poor hepatic reserve (odds ratio [OR] 4.630, 95% CI 2.887-7.425) and maximal tumor size > 5 cm (OR 5.788, 95% CI 3.192-10.495) remained independent risk factors for rHCC (**Table 2**). Because of confounding between BCLC stage and tumor characteristics (tumor size, PVTT, single or multiple tumors), we performed another multivariable analysis using BCLC stage instead of tumor characteristics. In this analysis, BCLC stage B (OR 4.448, 95% CI 1.896-10.434) and C (OR 6.666, 95% CI: 2.872-15.471) were also independent risk factors for rHCC (**Supplementary Table 1**).

Late rHCC is associated with worse OS; early rHCC is a protective factor before PSM

Univariate Cox regression analysis revealed that male sex, alcohol consumption, poor hepatic reserve, tumor rupture, AFP > 400 ng/mL, maximal tumor size > 5 cm, PVTT, and multiple tumors were associated with OS. Multivariable analysis revealed that poor hepatic reserve (hazard ratio [HR] 2.909, 95% CI 2.560-3.306), AFP > 400 ng/mL (HR 1.871, 95% CI 1.653-2.117), maximal tumor size > 5 cm (HR 2.082, 95% CI 1.826-2.37), PVTT (HR 1.932, 95% CI 1.685-2.215), and multiple tumors (HR 2.247, 95% CI 1.983-2.545) were independently associated with OS (**Supplementary Table 2**). Further multivariable analysis (using BCLC stage instead of tumor characteristics) revealed that BCLC stage B (HR 2.287, 95% CI: 1.957-2.672), stage C (HR 5.009, 95% CI 4.270-5.875), and stage D (HR 6.407, 95% CI 4.545-9.033) were independently associated with OS (**Supplementary Table 3**). rHCC (both early and late) was not associated with OS. Notably, late rHCC was an independent predic-

tor of worse OS (HR 1.578, 95% CI 1.059-2.351), and early rHCC was an independent predictor of better OS (HR 0.717, 95% CI 0.519-0.992) (**Table 3** and **Figure 2**). The distribution of early and late rHCC across different HCC stages is presented in **Supplementary Table 4**.

Treatment modality was significantly associated with OS. Multivariable Cox regression analysis revealed that surgical resection (HR 0.185, 95% CI 0.149-0.231), RFA (HR 0.355, 95% CI 0.279-0.453), TACE (HR 0.531, 95% CI 0.460-0.613), radiotherapy (HR 0.645, 95% CI 0.517-0.804), and systemic therapy (HR 0.814, 95% CI 0.689-0.961) were independently associated with better OS than were supportive care (**Supplementary Table 5**).

PSM

To isolate the effects of rHCC on health outcomes, we performed PSM to control for the confounders of early or late rHCC, sex, hepatic reserve, AFP levels, BCLC stage, and treatment modality.

Among patients with rHCC ($n = 102$), four were excluded due to missing data on AFP levels. In the matched cohort, 96, 92, 77, and 69 patients without rHCC were matched to patients with rHCC in the first, second, third, and fourth rounds of 1:4 matching, respectively, by using a strict caliper of 0.01. This resulted in a total of 98 patients with rHCC and 334 matched controls without rHCC (**Table 4**). No significant differences were observed in sex, hepatic reserve, AFP levels, BCLC stage distribution, or treatment modality, indicating balanced baseline characteristics between the groups.

Characteristics of patients with intermediate to advanced HCC and early or late rHCC

We investigated the effect of rupture timing in patients with intermediate to advanced HCC. Before PSM, patients with late rHCC were more likely to have poor hepatic reserve (77.4%) and AFP > 400 ng/mL (61.3%). Surgical resection was more prevalent among patients with inter-

Timing of spontaneous HCC rupture

Table 1. Demographic and baseline characteristics of patients with HCC with and without rHCC

Variable	Without rupture (n = 2,475)	With rupture (n = 102)	P value
Age (years)	65.0 (56.0-73.0)	60.0 (50.8-69.3)	.011
Sex (male), n (%)	1,785 (72.1)	75 (73.5)	.756
Etiology			
Hepatitis B virus, n (%)	1,227 (49.6)	51 (50.0)	.958
Hepatitis C virus, n (%)	958 (38.7)	26 (25.5)	.010
Alcohol, n (%)	673 (27.2)	33 (32.4)	.284
Diabetes mellitus, n (%)	903 (36.5)	35 (34.3)	.644
Cirrhosis, n (%)	1,520 (61.4)	54 (52.9)	.155
BCLC stage A/B/C/D, n (%)	1,016/681/663/115 (41.1/27.5/26.8/4.6)	7/27/58/10 (6.9/26.5/56.9/9.8)	< .001
Child-Pugh class A/B/C, n (%)	1,919/447/87 (77.5/18.1/3.5)	40/53/9 (39.2/52.0/8.8)	< .001
Total bilirubin (mg/dL)	0.9 (0.6-1.4)	1.2 (0.7-1.9)	.001
Albumin (g/dL)	4.0 (3.5-4.4)	3.4 (3.0-3.8)	< .001
Ascites, n (%)	485 (19.6)	70 (68.6)	< .001
Hepatic encephalopathy, n (%)	73 (2.9)	7 (6.9)	.026
AFP (ng/mL)	32.59 (5.80-729.83)	309.85 (29.47-12766.00)	< .001
> 400, n (%)	704 (28.4)	48 (47.1)	< .001
Tumor number			< .001
1	1,238 (50.0)	37 (36.3)	
2	342 (13.8)	7 (6.9)	
3	162 (6.5)	1 (1.0)	
≥ 4	730 (29.5)	57 (55.9)	
Tumor volume > 50%, n (%)	436 (17.6)	40 (39.2)	< .001
PVTT	632 (25.5)	47 (46.1)	< .001

Data are presented as median (interquartile range). AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombosis; rHCC: ruptured hepatocellular carcinoma.

mediate-stage HCC without rHCC and among patients with early rHCC than among patients with late rHCC: the rates of surgical resection in these groups were 27.6%, 15.5%, and 0%, respectively ([Supplementary Table 6](#)). After PSM, no significant differences in the proportion of Child-Pugh class B or C ($P = .878$) or AFP levels ($P = .432$) were observed among patients with intermediate-stage HCC. No patient with late rHCC received surgical resection. Patients with early or late rHCC were more likely to receive systemic therapy than those without rHCC ($P = .023$, [Supplementary Table 7](#)). Among patients with BCLC stage C, those with rHCC were younger, and those with late rHCC were significantly younger ($P = .001$) and were more likely to have PVTT (90.9%, $P = .001$) than were those with early rHCC ([Supplementary Table 8](#)).

Survival outcomes and prognostic factors

Kaplan-Meier analyses revealed significant differences in OS on the basis of BCLC stage and rHCC status (**Figure 3** and [Supplementary Table 4](#)). A subgroup analysis by rupture timing revealed that early rHCC was associated with worse OS compared with stage B cancer ($P = .001$) and better OS compared with stage C ($P = .003$), and that late rHCC was associated with worse OS compared with stage C ($P = .002$, **Figure 3A**). After PSM, OS did not differ significantly between patients with early rHCC and those without rHCC at BCLC stage B ($P = .594$), whereas patients with late rHCC had significantly worse OS than those without rHCC at BCLC stage B ($P = .007$; **Figure 3B**).

When patients with BCLC stage C were further stratified by rupture timing and PSM, patients

Timing of spontaneous HCC rupture

Table 2. Univariate and multivariable logistic regression analyses of factors associated with rHCC

Variable	Univariate analysis		Multivariable analysis	
	Odd ratio (95% CI)	P value	Odd ratio (95% CI)	P value
Age	0.981 (0.966-0.997)	.023	0.988 (0.971-1.005)	.171
Sex: male vs. female	1.074 (0.686-1.682)	.756		
Alcohol	1.261 (0.825-1.927)	.284		
Diabetes mellitus	0.907 (0.597-1.375)	.644		
Hepatitis B virus	1.011 (0.679-1.505)	.958		
Hepatitis C virus	0.552 (0.350-0.871)	.011	0.730 (0.436-1.221)	.230
Child-Pugh class: B or C vs. A	5.570 (3.701-8.384)	< .001	4.630 (2.887-7.425)	< .001
AFP > 400 vs. ≤ 400 ng/mL	2.388 (1.592-3.582)	< .001	1.196 (0.750-1.910)	.452
Maximal tumor size ≤ 5 vs. > 5 cm	6.688 (3.995-11.196)	< .001	5.788 (3.192-10.495)	< .001
PVTT	2.491 (1.670-3.714)	< .001	0.783 (0.469-1.307)	.349
Multiple vs. single tumor	1.762 (1.168-2.659)	.007	0.670 (0.402-1.119)	.126

AFP, α-fetoprotein; PVTT, portal venous tumor thrombosis; rHCC, ruptured hepatocellular carcinoma.

Table 3. Univariate and multivariable Cox regression analyses of factors associated with overall survival

Variable	Univariate analysis		Multivariable analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age (continuous)	0.997 (0.992-1.002)	.226		
Sex: male vs. female	1.235 (1.090-1.399)	.001	1.132 (0.988-1.296)	.073
Alcohol	1.232 (1.093-1.388)	.001	0.952 (0.836-1.084)	.457
Diabetes mellitus	0.964 (0.861-1.079)	.521		
Hepatitis B virus	1.002 (0.898-1.118)	.975		
Hepatitis C virus	0.929 (0.830-1.039)	.198		
Child-Pugh class: B or C vs. A	3.954 (3.512-4.452)	< .001	2.745 (2.407-3.130)	< .001
Tumor rupture				
≤ 7 days	1.733 (1.269-2.366)	.001	0.717 (0.519-0.992)	.044
> 7 days	5.186 (3.505-7.672)	< .001	1.578 (1.059-2.351)	.025
AFP > 400 vs. ≤ 400 ng/mL	3.208 (2.867-3.589)	< .001	1.986 (1.759-2.242)	< .001
BCLC stage				
B vs. A	2.633 (2.260-3.068)	< .001	2.300 (1.969-2.688)	< .001
C vs. A	7.881 (6.812-9.117)	< .001	5.018 (4.277-5.886)	< .001
D vs. A	17.940 (13.189-24.402)	< .001	6.084 (4.310-8.588)	< .001

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

with early rHCC had a comparable OS relative to those without rHCC ($P = .566$), and patients with late rHCC had worse OS relative to those without rHCC ($P = .006$, **Figure 3C**). Similarly, when patients with BCLC stages B and C were combined, OS was comparable between patients with early rHCC and those without rHCC ($P = .274$), whereas patients with late rHCC had significantly worse OS than those without rHCC ($P < .001$; **Figure 3D**).

Discussion

In this retrospective study, patients with rHCC had higher BCLC stages and worse hepatic reserve than those without rHCC. OS in patients with early rHCC was similar to that in patients with BCLC stages B and C, and OS in patients with late rHCC was worse than that in patients with BCLC stage C.

EASL guidelines specify prevention, surveillance, and treatment strategies for HCC in gen-

Timing of spontaneous HCC rupture

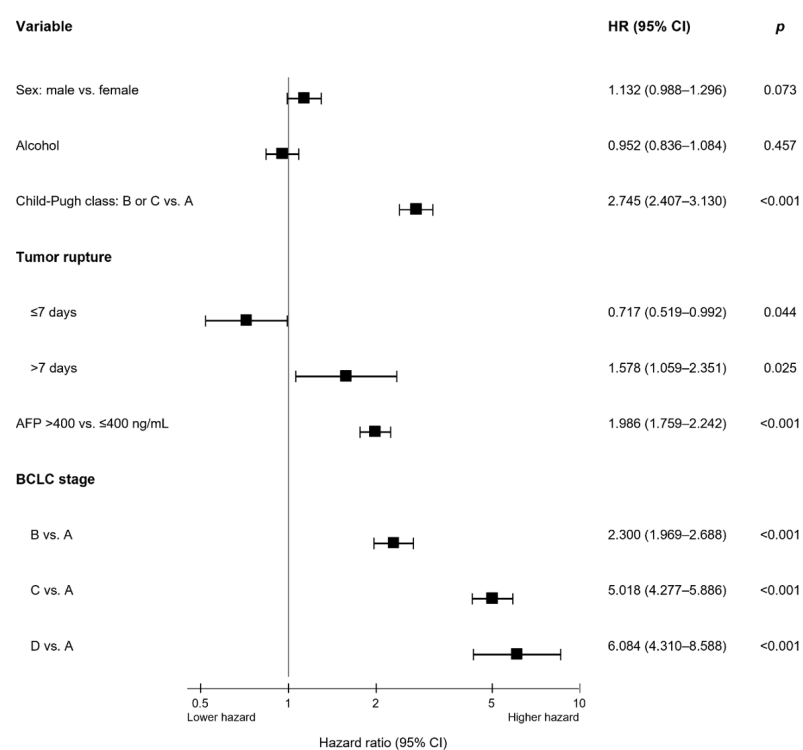


Figure 2. Forest plot of multivariable Cox regression analysis for factors associated with overall survival.

eral [16] - not for rHCC specifically. Similarly, the BCLC staging system lacks recommendations for this complication [10]. According to Sangro et al., existing guidelines cannot provide treatment recommendations because of limitations in current evidence and the complexity of rHCC [11]. Our findings highlight the effects of rupture timing, BCLC stage, and hepatic reserve on the prognosis of rHCC. Our study paves the way for further efforts to refine clinical strategies in patients with this life-threatening complication.

rHCC is a rare but life-threatening complication, with reported 30-day mortality rates ranging from 20%-70% [27, 28]. In Asia, rHCC varies in incidence from 2.3% to 26% [4]. In Western countries, the rHCC incidence is < 3% [29]. In the present study, 102 of 2,577 (4.0%) patients with HCC experienced rHCC. We further showed that tumor rupture, when considered as a whole, was not an independent predictor of OS. This finding is compatible with that of another study [30]. Nevertheless, other studies have demonstrated that tumor rupture negatively affects health outcomes [15, 31]. Furthermore, poor hepatic reserve (Child-Pugh class B or C)

and maximal tumor size > 5 cm were independent predictors of rHCC. These findings align with other studies that have demonstrated that larger tumor size [32, 33] and poor liver function [32, 33] are key risk factors. The present study did not observe any associations of OS with age, HBV infection [33], hypertension [6, 32], PVTT [6], or the presence of ascites [32]. Our study revealed that patients with rHCC, particularly those with late rHCC, were younger than those without rHCC (Table 1 and Supplementary Table 6). After PSM, patients with late rHCC at BCLC stage C were significantly more likely to be younger than those without rHCC or with early rHCC (Supplementary Table 8). Young age, high AFP levels, the presence of multiple tumors, and PVTT were associated with rHCC in the univariate analysis. This suggests that rHCC is related to more progressive tumors and thus predicts worse outcomes.

Poor hepatic reserve emerged as an independent predictor of reduced OS in our cohort. Other studies have also demonstrated that worse liver function is associated with limited treatment tolerability, increased perioperative risks, and increased short-term mortality [4, 32, 34]. Similarly, high AFP levels independently predicted poor OS, suggesting an association with aggressive tumor biology [35]. PVTT worsened OS by limiting therapeutic options and exacerbating disease progression, particularly in patients with compromised liver function [34, 35]. Multiple tumors, indicative of greater tumor burden, were also associated with worse OS [4, 28, 31]. OS was worse for patients with multiple tumors and nonruptured T4 HCC than for patients with rHCC but only a single tumor [4]. This suggests that tumor multiplicity drives aggressive tumor behavior, complicating management and reducing survival [28, 31]. Advanced BCLC stage at HCC diagnosis is asso-

Timing of spontaneous HCC rupture

Table 4. Demographic and baseline characteristics of patients with HCC with and without rHCC after PSM

Variable	Without rupture (n = 334)	With rupture (n = 98)	P value
Age (years)	66.0 (58.0-74.0)	60.0 (50.8-69.0)	< .001
Sex (male), n (%)	218 (65.3)	74 (75.5)	.057
Diabetes mellitus, n (%)	130 (38.9)	35 (35.7)	.565
BCLC stage A/B/C/D, n (%)	53/75/176/30 (15.9/22.5/52.7/9.0)	7/26/56/9 (7.1/26.5/57.1/9.2)	.174
Child-Pugh class A/B/C, n (%)	159/154/21 (47.6/46.1/6.3)	40/50/8 (40.8/51.0/8.2)	.462
Total bilirubin (mg/dL)	1.2 (0.7-2.0)	1.3 (0.7-2.0)	.656
Albumin (g/dL)	3.5 (3.0-4.1)	3.4 (3.1-3.8)	.431
AFP (ng/mL)	139.57 (12.78-3859.75)	309.85 (29.47-12766.00)	.113
> 400, n (%)	148 (44.3)	48 (49.0)	.414
PVTT, n (%)	167 (50.0)	46 (46.9)	.594
Treatment			
Surgical resection, n (%)	37 (11.1)	11 (11.2)	.968
RFA ± PEI, n (%)	17 (5.1)	2 (2.0)	.196
TACE, n (%)	206 (61.7)	67 (68.4)	.227
Systemic therapy, n (%)	63 (18.9)	24 (24.5)	.222
Radiotherapy, n (%)	10 (3.0)	5 (5.1)	.316

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; PSM, propensity score matching; PEI, percutaneous ethanol injection; PVTT, portal vein tumor thrombosis; RFA, radiofrequency ablation; rHCC, ruptured hepatocellular carcinoma; TACE, transarterial chemoembolization.

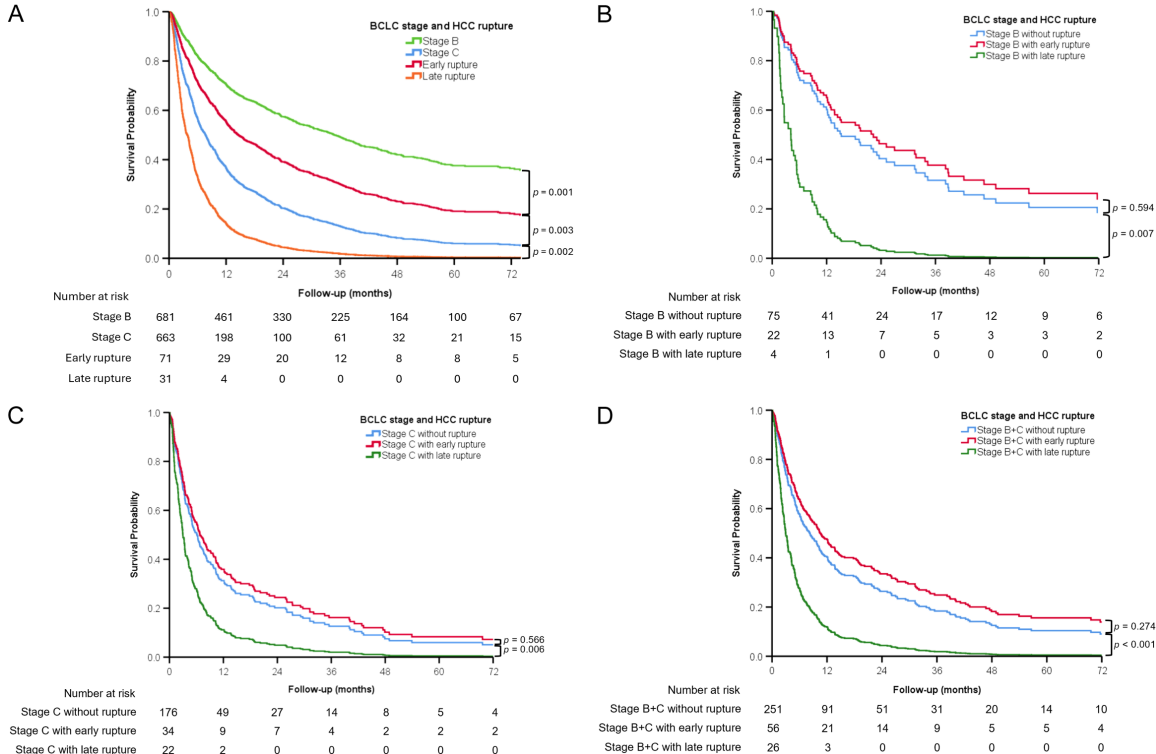


Figure 3. Kaplan-Meier analyses of overall survival. A. Early and late rupture before PSM. B. Early and late rHCC in patients with BCLC stage B after PSM. C. Early and late rHCC in patients with BCLC stage C after PSM. D. Early and late rHCC in patients with BCLC stage B+C after PSM. BCLC, Barcelona Clinic Liver Cancer; PSM, propensity score matching; rHCC, ruptured hepatocellular carcinoma.

ciated with significantly worse OS in patients with rHCC, reflecting increased tumor burden and compromised liver function. In our study, BCLC stages B, C, and D were independent predictors of worse OS, consistent with findings of other studies, which have demonstrated that advanced cancer is associated with reduced survival [4, 28, 34, 36]. Among patients with rHCC, median OS durations were 40 days for those with stage C cancer and 251 days for those with stage A cancer [37]. Incorporating BCLC stage into prognostic models enhances risk stratification, guiding individualized management to improve outcomes in this high-risk cohort [36].

Our study demonstrated that the prognostic implications of rHCC differed according to rupture timing. Among patients with BCLC stage C, those without rHCC and those with early rHCC had similar OS. Furthermore, OS among patients without rHCC and with early rHCC was significantly better than those with late rHCC ($P = .006$, **Figure 3C**). This pattern remained consistent when patients with BCLC stages B and C were analyzed together, with early rHCC associated with OS comparable to that of nonruptured HCC and late rHCC associated with significantly worse OS ($P < .001$, **Figure 3D**). Patients with early rHCC were more likely to have Child-Pugh class A (46.5%) and BCLC stage A (9.9%) or B (32.4%). Patients with late rHCC were less likely to have Child-Pugh class A (22.6%) and more likely to have BCLC stage C (71.0%) or D (16.1%), limiting treatment options. After PSM, late rHCC was associated with a significantly higher proportion of PVTT in patients with BCLC stage C ([Supplementary Table 8](#)), and patients with late rHCC were significantly younger than those with early rHCC or nonrupture in BCLC stage C ([Supplementary Table 8](#)). Among patients with early rHCC, 11 (15.5%), 1 (1.4%), and 55 (77.5%) received surgical resection, RFA, and TACE, respectively. Among patients with late rHCC, 1 (3.2%) and 14 (45.2%) received RFA and TACE, respectively ([Supplementary Table 6](#)). After PSM, patients with early rHCC and BCLC stage B were more likely to receive surgical resection and systemic therapy than those without rHCC or with late rHCC ([Supplementary Table 7](#)). Treatment modality was significantly associated with OS: surgical resection [11, 29, 34] and TACE [11] were independently associated with longer OS compared with supportive care.

Our PSM analysis partially mitigated measured confounding effects, including hepatic reserve, AFP level, BCLC stage, and treatment modality. We demonstrated that tumor characteristics and BCLC stage, rather than rupture status alone, drive prognoses. To the best of our knowledge, no studies have analyzed the effect of rupture timing on OS. Presumably, early rHCC may reflect a distinct tumor phenotype or diagnostic delay, yet its association with better OS may reflect rapid management in patients with relatively preserved liver function. Emerging evidence suggests that spontaneous HCC rupture may reflect not only tumor stage but also distinct biological and morphological characteristics. Tumor diameter was identified as a key predictor of spontaneous HCC rupture, and it was proposed that tumor-cell invasion and hepatic venous obstruction may increase intratumoral pressure, while venous congestion, central tumor necrosis, and intratumoral hemorrhage may further precipitate rupture [38]. Similarly, another study identified tumor diameter > 5 cm, macrovascular invasion, tumor protrusion, and $\text{AFP} \geq 400$ ng/mL as independent risk factors for spontaneous tumor rupture, suggesting that rupture may be closely linked to tumor morphology and biologic aggressiveness [39]. These observations may provide a biological explanation for the different prognostic implications of early and late rHCC observed in our study. Early rupture may represent a phenotype in which mechanical and morphological factors predisposing to rupture manifest before extensive tumor progression, whereas late rupture may more often occur in the setting of accumulated adverse tumor characteristics and poor liver reserve. Thus, the relatively favorable prognosis associated with early rHCC may not indicate that rupture itself is protective, but rather that the timing of rupture may capture differences in the underlying tumor biology and disease trajectory.

Late rHCC, conversely, may occur as a result of disease progression despite clinical care, and its worse prognosis likely reflects advanced BCLC stages and poor liver function, as seen in our cohort. These findings highlight rupture timing as a critical determinant of OS, with implications for risk stratification and treatment planning across BCLC stages.

The limitations of this study include its retrospective design, which may introduce selection

bias despite the use of PSM. Although immortal-time bias cannot be completely excluded, its influence is unlikely to fully account for our findings, as patients with late rHCC, who necessarily survived until rupture, nevertheless exhibited worse OS. The low incidence of rHCC meant that few cases were available for inclusion in our analysis. The lack of statistical significance in the survival analysis between early rHCC and nonruptured HCC might be a result of the small number of rHCC cases. The high HBV prevalence in our cohort may limit its generalizability to Western populations with diverse etiologies. External validation is needed to validate our findings. Finally, optimal therapeutic strategies for patients with rHCC remain to be established in future prospective studies.

In conclusion, this study demonstrated that the timing of spontaneous rHCC in relation to its clinical diagnosis significantly affects prognosis. Patients with early rHCC and those with unruptured HCC have similar OS outcomes; patients with late rHCC have worse outcomes, reflecting advanced disease and limited treatment options.

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Disclosure of conflict of interest

None.

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Timing of spontaneous HCC rupture

Supplementary Table 1. Univariate and multivariable logistic regression analyses of factors associated with rHCC

Variable	Univariate analysis		Multivariable analysis	
	Odd ratio (95% CI)	P value	Odd ratio (95% CI)	P value
Age (continuous)	0.981 (0.966-0.997)	.023	0.995 (0.978-1.013)	.587
Sex: male vs. female	1.074 (0.686-1.682)	.756		
Alcohol	1.261 (0.825-1.927)	.284		
Diabetes mellitus	0.907 (0.597-1.375)	.644		
Hepatitis B virus	1.011 (0.679-1.505)	.958		
Hepatitis C virus	0.552 (0.350-0.871)	.011	0.625 (0.376-1.037)	.069
Child-Pugh class: B or C vs. A	5.570 (3.701-8.384)	< .001	3.801 (2.398-6.027)	< .001
AFP > 400 vs. ≤ 400 ng/mL	2.388 (1.592-3.582)	< .001	1.108 (0.707-1.737)	.656
BCLC stage				
B vs. A	5.755 (2.492-13.289)	< .001	4.448 (1.896-10.434)	.001
C vs. A	12.697 (5.761-27.986)	< .001	6.666 (2.872-15.471)	< .001
D vs. A	12.621 (4.713-33.795)	< .001	3.020 (0.969-9.413)	.057

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; rHCC, ruptured hepatocellular carcinoma.

Supplementary Table 2. Univariate and multivariable Cox regression analyses of factors associated with overall survival

Variable	Univariate analysis		Multivariable analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age (continuous)	0.997 (0.992-1.002)	.226		
Sex: male vs. female	1.235 (1.090-1.399)	.001	1.030 (0.897-1.183)	.674
Alcohol	1.232 (1.093-1.388)	.001	0.932 (0.819-1.060)	.281
Diabetes mellitus	0.964 (0.861-1.079)	.521		
Hepatitis B virus	1.002 (0.898-1.118)	.975		
Hepatitis C virus	0.929 (0.830-1.039)	.198		
Child-Pugh class: B or C vs. A	3.954 (3.512-4.452)	< .001	2.909 (2.560-3.306)	< .001
Tumor rupture	2.331 (1.822-2.983)	< .001	1.123 (0.869-1.451)	.374
AFP ≥ 400 vs. < 400 ng/mL	3.208 (2.867-3.589)	< .001	1.871 (1.653-2.117)	< .001
Maximal tumor size > 5 vs. ≤ 5 cm	3.511 (3.140-3.926)	< .001	2.082 (1.826-2.373)	< .001
PVTT	4.786 (4.261-5.376)	< .001	1.932 (1.685-2.215)	< .001
Multiple vs. single tumor	3.410 (3.036-3.829)	< .001	2.247 (1.983-2.545)	< .001

AFP, alpha-fetoprotein; PVTT, portal venous tumor thrombosis.

Timing of spontaneous HCC rupture

Supplementary Table 3. Univariate and multivariable Cox regression analyses of factors associated with overall survival

Variable	Univariate analysis		Multivariable analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age (continuous)	0.997 (0.992-1.002)	.226		
Sex: male vs. female	1.235 (1.090-1.399)	.001	1.138 (0.993-1.303)	.062
Alcohol	1.232 (1.093-1.388)	.001	0.966 (0.849-1.099)	.594
Diabetes mellitus	0.964 (0.861-1.079)	.521		
Hepatitis B virus	1.002 (0.898-1.118)	.975		
Hepatitis C virus	0.929 (0.830-1.039)	.198		
Child-Pugh class: B or C vs. A	3.954 (3.512-4.452)	< .001	2.727 (2.392-3.109)	< .001
Tumor rupture	2.331 (1.822-2.983)	< .001	0.917 (0.711-1.184)	.508
AFP > 400 vs. ≤ 400 ng/mL	3.208 (2.867-3.589)	< .001	1.984 (1.758-2.239)	< .001
BCLC stage				
B vs. A	2.633 (2.260-3.068)	< .001	2.287 (1.957-2.672)	< .001
C vs. A	7.881 (6.812-9.117)	< .001	5.009 (4.270-5.875)	< .001
D vs. A	17.940 (13.189-24.402)	< .001	6.407 (4.545-9.033)	< .001

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

Supplementary Table 4. Comparison of BCLC stages among patients with non-ruptured HCC vs. early and late ruptured HCC

	Non-rupture (n = 2,475)	Early rupture (n = 71)	Late rupture (n = 31)
BCLC stage			
Stage A, n (%)	1,016 (41.1)	7 (9.9)	0 (0)
Stage B, n (%)	681 (27.5)	23 (32.4)	4 (12.9)
Stage C, n (%)	663 (26.8)	36 (50.7)	22 (71.0)
Stage D, n (%)	115 (4.6)	5 (7.0)	5 (16.1)

BCLC, Barcelona Clinic Liver Cancer.

Timing of spontaneous HCC rupture

Supplementary Table 5. Univariate and multivariable Cox regression analyses of factors associated with overall survival

Variable	Univariate analysis		Multivariable analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age (continuous)	0.997 (0.992-1.002)	.226		
Sex: male vs. female	1.235 (1.090-1.399)	.001	1.241 (1.082-1.422)	.002
Alcohol	1.232 (1.093-1.388)	.001	0.943 (0.828-1.073)	.370
Diabetes mellitus	0.964 (0.861-1.079)	.521		
Hepatitis B virus	1.002 (0.898-1.118)	.975		
Hepatitis C virus	0.929 (0.830-1.039)	.198		
Child-Pugh class: B or C vs. A	3.954 (3.512-4.452)	< .001	2.015 (1.755-2.313)	< .001
Tumor rupture	2.331 (1.822-2.983)	< .001	1.142 (0.881-1.480)	.315
AFP > 400 vs. ≤ 400 ng/mL	3.208 (2.867-3.589)	< .001	1.939 (1.715-2.193)	< .001
BCLC stage				
D vs. A	17.940 (13.189-24.402)	< .001	3.571 (2.493-5.117)	< .001
C vs. A	7.881 (6.812-9.117)	< .001	3.506 (2.869-4.285)	< .001
B vs. A	2.633 (2.260-3.068)	< .001	1.783 (1.491-2.133)	< .001
Treatment				
Surgical resection	0.238 (0.201-0.283)	< .001	0.185 (0.149-0.231)	< .001
RFA ± PEI	0.386 (0.325-0.460)	< .001	0.355 (0.279-0.453)	< .001
TACE	1.646 (1.475-1.837)	< .001	0.531 (0.460-0.613)	< .001
Radiotherapy	2.554 (2.077-3.141)	< .001	0.645 (0.517-0.804)	< .001
Systemic therapy	3.136 (2.743-3.586)	< .001	0.814 (0.689-0.961)	.015

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

Supplementary Table 6. Demographic and baseline characteristics of patients with BCLC stage B or C HCC without rHCC or with early or late rHCC before PSM

Variable	BCLC stage B without rupture (n = 681)	BCLC stage C without rupture (n = 663)	Rupture ≤ 7 days (n = 71)	Rupture > 7 days (n = 31)	P value
Age (years)	66.0 (57.0-74.0)	61.0 (53.0-70.0)	63.0 (54.0-75.0)	53.0 (44.0-64.0)	< .001
Sex (male), n (%)	513 (75.3)	523 (78.9)	49 (69.0)	26 (83.9)	.125
Diabetes mellitus, n (%)	224 (32.9)	211 (31.8)	21 (29.6)	14 (45.2)	.436
BCLC stage A/B/C/D, n (%)	0/681/0/0 (0/100/0/0)	0/0/663/0 (0/0/100/0)	7/23/36/5 (9.9/32.4/50.7/7.0)	0/4/22/5 (0/12.9/71.0/16.1)	< .001
Child-Pugh class A/B/C, n (%)	576/101/0 (84.6/14.8/0)	423/235/0 (63.8/35.4/0)	33/34/4 (46.5/47.9/5.6)	7/19/5 (22.6/61.3/16.1)	< .001
Total bilirubin (mg/dL)	0.8 (0.6-1.2)	1.1 (0.7-1.7)	1.0 (0.6-1.5)	1.7 (1.2-2.7)	< .001
Albumin (g/dL)	4.0 (3.5-4.4)	3.7 (3.3-4.1)	3.4 (3.0-3.8)	3.3 (3.0-4.1)	< .001
AFP (ng/mL)	28.44 (5.86-460.48)	829.93 (18.87-8845.50)	202.30 (16.10-15372.00)	570.08 (141.90-4199.00)	< .001
> 400, n (%)	178 (26.1)	355 (53.5)	29 (40.8)	19 (61.3)	< .001
PVTT	0 (0)	517 (78.0)	21 (29.6)	26 (83.9)	< .001
Treatment					
Surgical resection, n (%)	188 (27.6)	44 (6.6)	11 (15.5)	0 (0)	< .001
RFA ± PEI, n (%)	30 (4.4)	7 (1.1)	1 (1.4)	1 (3.2)	.002
TACE, n (%)	377 (55.4)	278 (41.9)	55 (77.5)	14 (45.2)	< .001
Systemic therapy, n (%)	19 (2.8)	313 (47.2)	13 (18.3)	11 (35.5)	< .001
Radiotherapy, n (%)	8 (1.2)	102 (15.4)	1 (1.4)	4 (12.9)	< .001

Data are presented as median (first quartile to third quartile). AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; PEI, percutaneous ethanol injection; PSM, propensity score matching; PVTT, portal vein tumor thrombosis; RFA, radiofrequency ablation; rHCC, ruptured hepatocellular carcinoma; TACE, transarterial chemoembolization.

Timing of spontaneous HCC rupture

Supplementary Table 7. Demographic and baseline characteristics of patients with BCLC stage B HCC without rHCC or with early or late rHCC after PSM

Variable	BCLC stage B without rupture (<i>n</i> = 75)	BCLC stage B with rupture ≤ 7 days (<i>n</i> = 22)	BCLC stage B with rupture > 7 days (<i>n</i> = 4)	<i>P</i> value
Age (years)	68.0 (59.0-76.0)	68.0 (64.0-78.3)	59.5 (48.5-73.5)	.369
Sex (male), <i>n</i> (%)	51 (68.0)	19 (86.4)	4 (100.0)	.108
Diabetes mellitus, <i>n</i> (%)	27 (36.0)	9 (40.9)	2 (50.0)	.800
Child-Pugh score A/B/C, <i>n</i> (%)	40/35/0 (53.3/46.7/0)	13/9/0 (59.1/40.9/0)	2/2/0 (50/50/0)	.878
Total bilirubin (mg/dL)	1.1 (0.8-1.6)	1.0 (0.7-1.2)	1.7 (0.7-9.8)	.138
Albumin (g/dL)	3.3 (2.9-4.0)	3.6 (3.2-3.9)	3.4 (3.2-3.8)	.662
AFP (ng/mL)	84.85 (8.08-2512.01)	138.21 (13.49-13098.75)	2171.76 (103.28-38372.75)	.432
> 400, <i>n</i> (%)	29 (38.7)	9 (40.9)	2 (50.0)	.894
Treatment				
Surgical resection, <i>n</i> (%)	6 (8.0)	6 (27.3)	0 (0)	.037
RFA ± PEI, <i>n</i> (%)	1 (1.3)	1 (4.5)	0 (0)	.610
TACE, <i>n</i> (%)	66 (88.0)	19 (86.4)	2 (50)	.101
Systemic therapy, <i>n</i> (%)	5 (6.7)	6 (27.3)	1 (25)	.023
Radiotherapy, <i>n</i> (%)	0 (0)	0 (0)	0 (0)	.

Data are presented as median (first quartile to third quartile). AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; PEI, percutaneous ethanol injection; PSM, propensity score matching; PVTT, portal vein tumor thrombosis; RFA, radiofrequency ablation; rHCC, ruptured hepatocellular carcinoma; TACE, transarterial chemoembolization.

Supplementary Table 8. Demographic and baseline characteristics of patients with BCLC stage C HCC without rHCC or with early or late rHCC after PSM

Variable	BCLC stage C without rupture (<i>n</i> = 176)	BCLC stage C with rupture ≤ 7 days (<i>n</i> = 34)	BCLC stage C with rupture > 7 days (<i>n</i> = 22)	<i>P</i> value
Age (years)	63.0 (55.0-72.0)	58.5 (49.8-68.5)	51.5 (42.8-64.0)	.001
Sex (male), <i>n</i> (%)	126 (71.6)	23 (67.6)	17 (77.3)	.738
Diabetes mellitus, <i>n</i> (%)	65 (36.9)	6 (17.6)	9 (40.9)	.077
Child-Pugh score A/B/C, <i>n</i> (%)	76/100/0 (43.2/56.8/0)	14/20/0 (41.2/58.8/0)	5/17/0 (22.7/77.3/0)	.184
Total bilirubin (mg/dL)	1.2 (0.8-2.0)	1.1 (0.7-1.7)	1.5 (1.2-2.4)	.093
Albumin (g/dL)	3.5 (3.1-4.0)	3.3 (3.0-3.7)	3.4 (3.1-4.1)	.274
AFP (ng/mL)	1049.67 (19.49-10940.50)	1327.18 (54.55-35838.00)	579.75 (288.09-22704.75)	.504
> 400, <i>n</i> (%)	97 (55.1)	19 (55.9)	15 (68.2)	.506
PVTT	140 (79.5)	18 (52.9)	20 (90.9)	.001
Treatment				
Surgical resection, <i>n</i> (%)	7 (4.0)	3 (8.8)	0 (0)	.257
RFA ± PEI, <i>n</i> (%)	2 (1.1)	0 (0)	0 (0)	.725
TACE, <i>n</i> (%)	120 (68.2)	25 (73.5)	11 (50)	.161
Systemic therapy, <i>n</i> (%)	55 (31.3)	7 (20.6)	10 (45.6)	.144
Radiotherapy, <i>n</i> (%)	10 (5.7)	1 (2.9)	4 (18.2)	.053

Data are presented as median (first quartile to third quartile). AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; PEI, percutaneous ethanol injection; PSM, propensity score matching; PVTT, portal vein tumor thrombosis; RFA, radiofrequency ablation; rHCC, ruptured hepatocellular carcinoma; TACE, transarterial chemoembolization.