


Splenectomy before hepatectomy for patients with hepatocellular carcinoma and hypersplenism

A retrospective study

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Abstract

The spleen plays an important role in tumor progression and the curative effects of splenectomy before hepatectomy for hypersplenism and hepatocellular carcinoma (HCC) are not clear. We investigated whether splenectomy before hepatectomy increases survival rate among patients with HCC and hypersplenism compared with that of patients who underwent synchronous hepatectomy and splenectomy or hepatectomy alone.

Between January 2011 and December 2016, 266 patients who underwent hepatectomy as a result of HCC and portal hypertension secondary to hepatitis were retrospectively analyzed. Their perioperative complications and survival outcome were evaluated.

Patients underwent synchronous hepatectomy and splenectomy (H-S group) and underwent splenectomy before hepatectomy (H-preS group) exhibited significantly higher disease-free survival (DFS) rates than those of patients underwent hepatectomy alone (H-O group). The DFS rates for patients in the H-S group, H-preS group, and H-O group were 74.6%, 48.4%, 39.8%, and 80.1%, 54.2%, 40.1%, and 60.5%, 30.3%, 13.3%, at 1, 3, and 5 years after surgery, respectively. Tumor size, tumors number, and levels of alpha fetoprotein (AFP) were independent risk factors for DFS. Gender and tumor size were independent prognostic factor for overall survival (OS). The preoperative white blood cell (WBC) and platelet (PLT) counts were significantly higher in the H-preS group than in those of the H-S group and the H-O group. After operation, the WBC and PLT counts in the H-S group and H-preS groups were significantly higher compared to those of the H-O group.

No matter splenectomy before hepatectomy or synchronous hepatectomy and splenectomy, hepatectomy with splenectomy may improve DFS rates in patients with HCC and hypersplenism, and splenectomy before hepatectomy alleviates hypersplenism without an increased surgical risk.

Abbreviations: AFP = alpha fetoprotein, ANCOVA = analysis of covariance, BCLC = Barcelona Clinic Liver Cancer, BMI = body mass index, CI = confidence interval, CT = computed tomography, DFS = disease-free survival, HBV = hepatitis B virus, HBV-DNA = hepatitis B virus deoxyribonucleic acid, HCC = hepatocellular carcinoma, HR = hazard ratio, IQR = interquartile range, MRI = magnetic resonance imaging, OS = overall survival, PLT = platelet, TACE = transcatheter arterial chemoembolization, WBC = white blood cell.

Keywords: hepatectomy, hepatocellular carcinoma, retrospective study, splenectomy

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Hepatocellular carcinoma (HCC) is a common malignant tumor around the world. About 50% of the total number of HCC cases come from China. Eighty-five percent to 90% of HCC cases are associated with cirrhosis of different degrees, and about 30% of the cases are accompanied by hypersplenism.^[1,2] Hypersplenism secondary to portal hypertension can induce liver function injury and increase risk of hemorrhage, which can limit the possibilities for most curative treatments and affects the prognosis.^[3] There are several approaches used to treat hypersplenism. Splenectomy, either open or laparoscopy, is an effective treatment for hypersplenism and portal hypertension.^[4] But there are no data showing that correcting the hypersplenism increases patient survival rates.^[5]

The spleen plays an important role in the immune system. Some researchers found that the spleen has 2-way regulation on tumor progression.^[6] On one hand, in the early stage of the disease, the spleen produced lymphokines and antibodies to suppress the tumor progression. On the other hand, as the tumors grew, tumor-derived factors changed the microenvironment and the immunosuppressive and tumor-promoting functions of the spleen gradually increased.^[7–10]

Several studies reported that splenectomy combined with hepatectomy could extend disease-free survival (DFS) and overall survival (OS) rate.^[11–15] But there are no data about the use of splenectomy before hepatectomy and the curative effects of this treatment for hypersplenism and HCC are not clear. In this study, we aimed to investigate whether the use of splenectomy before hepatectomy increases survival rates of patients with HCC and hypersplenism compared with those of patients receiving synchronous hepatectomy and splenectomy or hepatectomy alone.

2. Methods

2.1. Patients

Between January 2011 and December 2016 in the Hepatic Surgery Center of Tongji Hospital, Wuhan, China, 266 patients diagnosed with HCC and portal hypertension secondary to hepatitis who underwent hepatectomy were retrospectively analyzed. Splenectomy before hepatectomy was defined as the splenectomy carried out >1 month before hepatectomy. The patients were divided into 3 groups. One hundred three of 266 patients underwent synchronous hepatectomy and splenectomy (H-S group), 41 of 266 patients underwent splenectomy before hepatectomy (H-preS group), and 122 patients underwent hepatectomy alone (H-O group). Inclusion criteria included ages from 18 to 75 years, male or female; splenomegaly and hypersplenism [(I) imaging confirmed splenomegaly, (II) platelet (PLT) <120 × 10⁹/L] or history of splenectomy due to hypersplenism; HCC, Barcelona Clinic Liver Cancer (BCLC) stage A or B; No serious organic diseases of the heart, lungs, brain, or other organs; and No radiological, chemical, or immunological therapies before surgery. Exclusion criteria included absence of clinical data; history of organ transplantation; and history of other malignancies. This study was approved by the Medical Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. This study was conducted according to the Declaration of Helsinki. The requirement for the written informed patient consent was waived due to the retrospective and anonymous nature of this study. The information of all the patients were only used for analysis.

2.2. Data collection

Clinical data of the patients were recorded. The following clinical variables were collected: age, gender, etiology, blood type, history of abdominal surgery, body mass index (BMI), Child-Pugh score on admission, Clavien-Dindo classification of postoperative complications.^[16] The following laboratory data were collected during the perioperative period: routine blood count, liver function, coagulation test, serum tumor marker. The following data during operation were also recorded: duration of the total hospital stay, operative time, type of surgery, extent of liver resection, intraoperative blood loss, intraoperative blood transfusion, and portal triad clamping time.

2.3. Surgical indication

Indications for hepatectomy included normal liver function (Child-Pugh grade A or Child-Pugh grade B, which can be corrected to Child-Pugh grade A); single or multiple tumors localized in 2 to 3 neighboring segments; enough residual liver volume; and no vascular invasion, or lymph node or extrahepatic metastases. Indications for splenectomy include history of variceal bleeding; portal hypertension with serum platelet level less than 50 × 10⁹/L; and hypersplenism combined with “red sign” in the gastroscopy.

2.4. Follow-up

All patients were followed up with blood routine examination, liver function test, tumor marker measurement, liver ultrasonography, enhanced computed tomography (CT) or magnetic resonance imaging (MRI), and chest X-ray every month within the half year post operation, every 2 months during the following 2 years, and every 3 months thereafter. Antiviral treatment continued until serum virology was completely clear. Patients with recurrence or local tumor progression were scheduled for further treatment. Treatments for patients with recurrence or metastasis were determined by tumor characteristics, patient preference, and the suggestion of a multidisciplinary team. The treatments include repeat liver resection, local ablation therapy, transcatheter arterial chemoembolization (TACE), external radiation therapy, targeted therapy, immunotherapy, or support therapy.

2.5. Statistical analysis

Continuous variables were expressed as median with interquartile range (IQR) and were compared between groups using Kruskal–Wallis H test for variables with an abnormal distribution. Repeated measures were analyzed by analysis of covariance (ANCOVA). Categorical variables are compared using the χ^2 -test or Fisher exact test as applicable. DFS was defined as the interval between the date of operation and the detection of tumor recurrence. OS was measured from the date of operation until the date of tumor-related death. The DFS rates and OS rates were analyzed using the Kaplan–Meier method, and the differences between groups were analyzed using the log-rank test. The Cox proportional hazard model was used for univariate and multivariate analyses of factors influencing prognosis. Two-tailed *P* values ≤ .05 were considered statistically significant. Calculations were performed using the SPSS version 26.0 (IBM, Armonk, NY).

3. Result

3.1. Baseline characteristics

All patients exhibited a pathological spleen. Patients in H-S group and H-preS group underwent splenectomy and hepatectomy, whereas patients in H-O group underwent hepatectomy alone. The basic information for 3 groups is listed in Table 1.

The majority of patients in this study had hepatitis B virus (HBV) infection, accounting for 98.1%, 87.8%, 91.8% of the patients, respectively ($P=.089$). Most cases in H-S group and H-O group had positive HBV deoxyribonucleic acid (HBV-DNA) copies, while more than half of the cases in H-preS group had negative HBV-DNA copies ($P=.006$). Patients in H-S group had more ascites ($P=.004$) and poorer liver function ($P=.032$) on admission. HBV-DNA, ascites, and liver function were corrected to the same level before surgery. Other demographics and tumor-related characteristics were balanced between the groups.

3.2. Perioperative data

The intraoperative variables are summarized in Table 2. Most patients in H-S group and H-preS group underwent open surgery, while in H-O group the proportion went down ($P<.001$). In this study, only a small portion of patients received anatomic resection and most patients received partial liver resection. During the surgery, blood loss of patients in H-S group was more severe than that of patients in the H-preS group and H-O group

($P<.001$), so more patients in the H-S group needed intraoperative blood transfusion ($P<.001$). In addition, the length of hospital stays for patients in the H-S group were prolonged ($P<.006$).

3.3. Postoperative complications

According to Clavien-Dindo classification, the postoperative complications are summarized in Table 3. Complications above grade III, defined as major complications, were analyzed. Twenty patients (19.4%) in the H-S group, 4 patients (9.8%) in the H-preS group, and 16 patients (13.1%) in the H-O group developed postoperative complications of grade III or higher. There was 1 in-hospital death in H-S group and H-O group. However, no significant difference in the classification of complications was noted between the 3 groups ($P=.673$).

3.4. Laboratory tests

The preoperative white blood cell (WBC) and PLT counts were significantly higher in the H-preS group than in the H-S group and the H-O group. After operation, the WBC and PLT counts in the H-S group and H-preS group were significantly higher than the H-O group (Both $P<.001$, Figs. 1 and 2). There was no significant difference in the levels of total bilirubin levels between the H-S group and the H-O group or the H-preS group and the H-O group ($P=.415$, $.902$, respectively, Fig. 3).

Table 1
Baseline characteristics of H-S group, H-preS group, and H-O group.

Variable	H-S group (N=103)	H-preS group (N=41)	H-O group (N=122)	P
Age, yr	51 (43–58)	53 (44–58)	52 (45–60)	.557
Gender				
Male	77 (74.8%)	34 (82.9%)	102 (83.6%)	.224
Female	26 (25.2%)	7 (17.1%)	20 (16.4%)	
Tumor size, cm	3.5 (2.6–4.4)	3.3 (2.4–4.95)	3.3 (2.375–5.0)	.859
>5	19 (18.4%)	10 (24.4%)	32 (26.2%)	.373
≤5	84 (81.6%)	31 (75.6%)	90 (73.8%)	
Tumor number				
Single	94 (91.3%)	37 (90.2%)	107 (87.7%)	.714
Multiple	9 (8.7%)	4 (9.8%)	15 (12.3%)	
ASA				
I	17 (16.5%)	6 (14.6%)	18 (14.8%)	.980
II	78 (75.7%)	32 (78%)	92 (75.4%)	
III	8 (7.8%)	3 (7.3%)	12 (9.8%)	
Etiology				
HBV	101 (98.1%)	36 (87.8%)	112 (91.8%)	.089
HCV	1 (1.0%)	2 (4.9%)	4 (3.3%)	
Schistosomiasis	0 (0%)	2 (4.9%)	1 (0.8%)	
Other	1 (1.0%)	1 (2.4%)	5 (4.1%)	
HBV-DNA copies				
Positive	76 (73.8%)	19 (46.3%)	75 (61.5%)	.006
Negative	27 (26.2%)	22 (53.7%)	47 (38.5%)	
Ascites				
Positive	32 (31.1%)	5 (12.2%)	18 (14.8%)	.004
Negative	71 (68.9%)	36 (87.8%)	104 (85.2%)	
Child-Pugh class				
A	86 (83.5%)	37 (90.2%)	115 (94.3%)	.032
B	17 (16.5%)	4 (9.8%)	7 (5.7%)	
AFP, ng/mL	81.3 (16.2–1326.2)	55.6 (7.79–167.1)	46.5 (7.4–692.8)	.157
ICG R-15, %	10.7 (4.0–20.1)	9.0 (4.75–15.7)	7.9 (4.3–14.9)	.250

Data are expressed as n (%) or median (IQR).

AFP=alpha fetoprotein, ASA=American Society of Anesthesiologists, HBV=hepatitis B virus, HCV=hepatitis C virus, ICG R-15=indocyanine green retention rates at 15 min, IQR=interquartile ranges.

Table 2
Perioperative data of H-S group, H-preS group, and H-O group.

Variable	H-S group (N=103)	H-preS group (N=41)	H-O group (N=122)	P
Surgical procedure				
Laparoscopic surgery	8 (7.8%)	6 (14.6%)	46 (37.7%)	<.001
Open surgery	95 (92.2%)	35 (85.4%)	76 (62.3%)	
Anatomic resection				
Positive	10 (9.7%)	5 (12.2%)	27 (22.1%)	.031
Negative	93 (90.3%)	36 (87.8%)	95 (77.9%)	
Operative time, min	278 (243–328)	230 (186–293)	216 (183.5–275)	<.001
Estimated blood loss, mL	395.34 ± 389.72	246.59 ± 244.14	252.30 ± 279.96	<.001
Intraoperative blood transfusion				
Positive	42 (40.8%)	7 (17.1%)	10 (8.2%)	<.001
Negative	61 (59.2%)	34 (82.9%)	112 (91.8%)	
Cholecystectomy				
Positive	22 (78.6%)	13 (31.7%)	34 (27.9%)	.355
Negative	81 (21.4%)	28 (68.3%)	88 (72.1%)	
Hepatectomy				
Partial	79 (76.7%)	34 (82.9%)	86 (73.0%)	.441
1 Segmentectomy	7 (6.8%)	1 (2.4%)	6 (4.9%)	
2 Segmentectomy	14 (13.6%)	3 (7.3%)	21 (17.2%)	
3 Segmentectomy	3 (2.9%)	2 (4.9%)	6 (4.9%)	
4 Segmentectomy	0 (0%)	1 (2.4%)	0 (0%)	
Hepatic inflow occlusion				
Positive	22 (21.4%)	8 (19.5%)	39 (32.0%)	.116
Negative	81 (78.6%)	33 (80.5%)	83 (68.0%)	
Hospital stays, d	24 (21–30)	19 (15.5–23)	18 (15–22)	<.001

Data are expressed as n (%) or median (IQR).

Table 3
Postoperative complications classified by Clavien-Dindo classification for the 3 groups.

Clavien-Dindo classification	H-S group (N=103)	H-preS group (N=41)	H-O group (N=122)	P
Grade I	71 (68.9%)	34 (82.9%)	98 (80.3%)	.673
Grade II	12 (11.7%)	3 (7.3%)	8 (6.6%)	
Grade III*	17 (16.5%)	4 (9.8%)	13 (10.7%)	
Grade IV†	2 (1.9%)	0 (0%)	2 (1.6%)	
Grade V‡	1 (1.0%)	0 (0%)	1 (0.8%)	

* H-S group: 14 patients received thoracentesis due to pleural effusion, 2 patients received abdominocentesis due to bile leakage; 1 patient underwent reoperation for uncontrolled intraabdominal hemorrhage. H-preS group: 4 patients received thoracentesis due to pleural effusion; H-O group: 11 patients received thoracentesis due to pleural effusion, 1 patient suffered dehiscence of abdominal incision and another patient suffered from arytenoid dislocation, both of them received reoperation.

† In the H-S group and H-O group, 2 patients required ICU management due to liver failure, respectively.

‡ In the H-S group and H-O group, 1 patient died from liver failure, respectively.

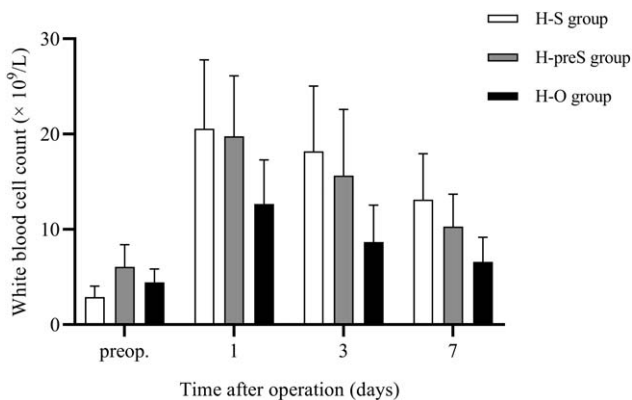


Figure 1. Mean (s.d.) preoperative and postoperative white blood cell counts in patients of H-S group, H-preS group, and H-O group. WBC counts in the H-S group and H-preS group were significantly higher than those in the H-O group after operation (Both $P < .001$).

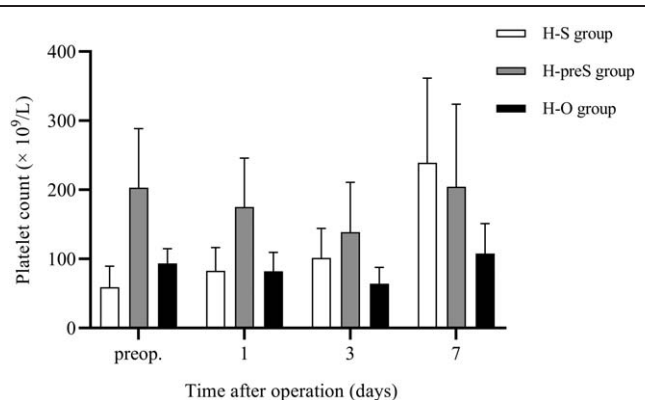


Figure 2. Mean (s.d.) preoperative and postoperative platelet counts in patients of H-S group, H-preS group, and H-O group. Plt counts in the H-S group and H-preS group were significantly higher than those in the H-O group after operation (Both $P < .001$).

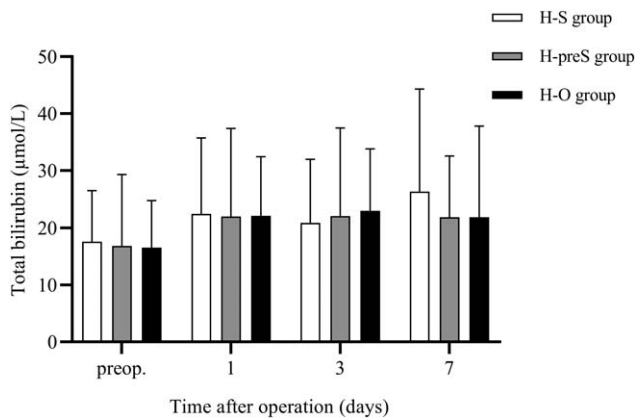


Figure 3. Mean (s.d.) preoperative and postoperative total bilirubin in patients of H-S group, H-preS group, and H-O group. There was no significant difference in the levels of total bilirubin between the H-S group and the H-O group or the H-preS group and the H-O group ($P = .415, .902$, respectively).

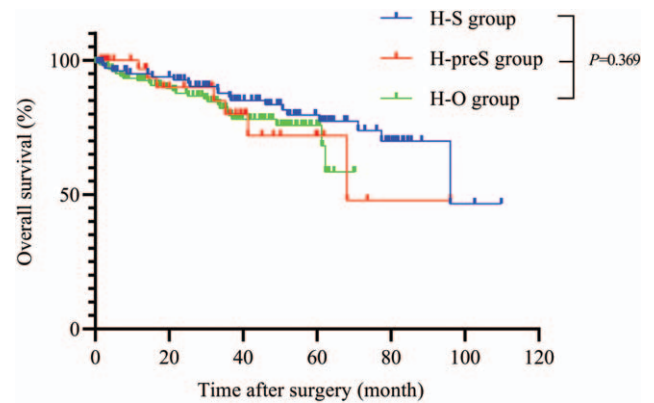


Figure 5. Overall survival rates of patients in the three groups. The 1-, 3-, and 5-year overall survival rates for patients in the H-S group, H-preS group, and H-O group were 94.9%, 87.7%, 79.7%, and 96.8%, 79.9%, 71.9% and 92.4%, 80.8%, 75.7%, respectively. No significant difference in overall survival was noted between the groups ($P = .396$).

3.5. Survival rate

Patients in H-S group exhibited a significantly higher DFS rate than patients in the H-O group. The 1-, 3-, and 5-year DFS rates for patients in the H-S group and H-O group were 74.6%, 48.4%, 39.8%, and 60.5%, 30.3%, 13.3%, respectively ($P = .001$, Fig. 4). DFS rate was also higher in the H-preS group than in the H-O group. The 1-, 3-, and 5-year DFS rates for patients in the H-preS group and H-O group were 80.1%, 54.2%, 40.1%, and 60.5%, 30.3%, 13.3%, respectively ($P = .006$, Fig. 4). The 1-, 3-, and 5-year OS rates for patients in the H-S group H-preS group and H-O group were 94.9%, 87.7%, 79.7%, and 96.8%, 79.9%, 71.9% and 92.4%, 80.8%, 75.7%, respectively. There was, however, no significant difference in the OS rates between the groups ($P = .396$, Fig. 5).

3.6. Prognostic factors for patients with HCC and portal hypertension

Univariate and multivariate analyses demonstrated that tumor size $>5\text{cm}$ [hazard ratio (HR) 1.534, 95% confidence interval (95% CI) 1.065–2.210, $P = .021$], multiple tumors (HR 2.077, 95% CI 1.323–3.262, $P = .002$), alpha fetoprotein (AFP) $>400\text{ ng/mL}$ (HR 1.498, 95% CI 1.065–2.109, $P = .020$), and splenectomy (HR 0.590, 95% CI 0.419–0.831, $P = .003$) were independent risk factor for DFS in patients with HCC and portal hypertension (Table 4). In univariate analysis for OS, being male (HR 2.914, 95% CI 1.154–7.357, $P = .024$), tumor size $>5\text{ cm}$ (HR 2.324, 95% CI 1.307–4.132, $P = .004$), and AFP $>400\text{ ng/mL}$ (HR 1.759, 95% CI 1.006–3.077, $P = .048$) were independent prognostic factor of patients with HCC and portal hypertension. In multivariate analysis for OS, being male (HR 3.123, 95% CI 1.228–7.943, $P = .017$), tumor size $>5\text{ cm}$ (HR 2.053, 95% CI 1.118–3.771, $P = .020$) were independent prognostic factors of patients with HCC and portal hypertension (Table 5).

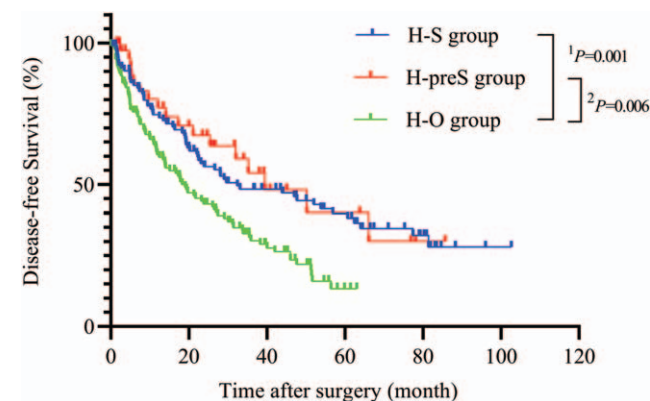


Figure 4. Disease-free survival rates of patients in the 3 groups. Patients in the H-S group exhibited a significantly higher disease-free survival rate than patients in the H-O group (The 1-, 3-, and 5-year disease-free survival rates: 74.6%, 48.4%, 39.8%, vs 60.5%, 30.3%, 13.3%, $*P = .001$). Disease-free survival was also higher in the H-preS group compared to the H-O group (The 1-, 3-, and 5-year disease-free survival rates: 80.1%, 54.2%, 40.1%, vs 60.5%, 30.3%, 13.3%, respectively, $^{\dagger}P = .006$).

4. Discussion

In the present study, we evaluated prognosis of patients with HCC and hypersplenism, and found that no matter splenectomy before hepatectomy or synchronous hepatectomy and splenectomy, hepatectomy with splenectomy can prolong the DFS for patients with HCC and hypersplenism. The postoperative complications of splenectomy before hepatectomy are acceptable compared with those of other groups. We suggest that splenectomy before hepatectomy are safe and beneficial for selected patients with HCC and portal hypertension.

Hypersplenism is common in patients with portal hypertension, suggesting the likelihood of a more advanced liver disease and an increased risk of complications. Splenectomy is effective in improving white blood counts and platelet counts and is usually regarded as the optimum choice to treat hypersplenism.^[4] Liver transplantation is recommended and liver resection is contraindicated due to a very high risk of post hepatectomy liver failure and mortality for patients with HCC and portal

Table 4
Univariate and multivariate analyses of prognostic factors for disease-free survival.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender (male vs female)	1.250 (0.849–1.842)	.258		
Age (>50 vs ≤50 yr)	1.175 (0.860–1.604)	.311		
Tumor size (>5 vs ≤5 cm)	1.763 (1.243–2.502)	.001	1.534 (1.065–2.210)	.021
Tumor number (multiple vs single)	2.317 (1.482–3.621)	<.001	2.077 (1.323–3.262)	.002
HBV-DNA (positive vs negative)	1.005 (0.728–1.387)	.978		
AFP (>400 vs ≤400 ng/mL)	1.407 (1.016–1.949)	.040	1.498 (1.065–2.109)	.020
Child-Pugh class (A vs B)	1.117 (0.684–1.825)	.659		
Splenectomy* (yes vs no)	0.536 (0.391–0.736)	<.001	0.590 (0.419–0.831)	.003
Hepatectomy (segmentectomy vs partial)	1.395 (0.983–1.979)	.062	1.381 (0.965–1.976)	.078
Intraoperative blood transfusion (yes vs no)	0.693 (0.471–1.019)	.062	0.813 (0.535–1.235)	.331
Hepatic inflow occlusion (yes vs no)	1.100 (0.774–1.564)	.594		

AFP = alpha fetoprotein, CI = confidence interval, HBV-DNA = hepatitis B virus deoxyribonucleic acid, HR = hazard ratio.

* Splenectomy included splenectomy before hepatectomy and synchronous hepatectomy and splenectomy.

Table 5
Univariate and multivariate analyses of prognostic factors for overall survival.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender (male vs female)	2.914 (1.154–7.357)	.024	3.123 (1.228–7.943)	.017
Age (>50 vs ≤50 yr)	1.001 (0.579–1.728)	.998		
Tumor size (>5 vs ≤5 cm)	2.324 (1.307–4.132)	.004	2.053 (1.118–3.771)	.020
Tumor number (multiple vs single)	2.019 (0.902–4.520)	.088	1.789 (0.780–4.103)	.170
HBV-DNA (positive vs negative)	0.965 (0.536–1.739)	.907		
AFP (>400 vs ≤400 ng/mL)	1.759 (1.006–3.077)	.048	1.668 (0.933–2.981)	.084
Child-Pugh class (A vs B)	0.725 (0.341–1.544)	.404		
Splenectomy* (yes vs no)	0.709 (0.401–1.254)	.237	0.835 (0.446–1.562)	.572
Hepatectomy (segmentectomy vs partial)	1.348 (0.728–2.496)	.342	1.278 (0.681–2.399)	.445
Intraoperative blood transfusion (yes vs no)	1.110 (0.596–2.070)	.742	1.072 (0.546–2.101)	.841
Hepatic inflow occlusion (yes vs no)	0.982 (0.524–1.841)	.955		

AFP = alpha fetoprotein, CI = confidence interval, HBV-DNA = hepatitis B virus deoxyribonucleic acid, HR = hazard ratio.

* Splenectomy included splenectomy before hepatectomy and synchronous hepatectomy and splenectomy.

hypertension.^[17–19] Nevertheless, the lack of organ donors limits the use of liver transplantation and alternative treatments on these patients. Furthermore, some studies indicated that synchronous splenectomy and hepatectomy could extend DFS and OS, but indications and preparation of operation may be strict and patients with poor physical conditions cannot tolerate this operation. If splenectomy is carried out at the early stage and hepatectomy after the occurrence of HCC, condition of patients could improve and the patients may be able to tolerate liver resection. To evaluate this surgical procedure and decrease biases, we evaluated potential confounding variables that may affect prognosis. Univariate and multivariate analyses demonstrated that tumor size, tumor number, levels of AFP were independent risk factor for DFS. Baseline levels of these factors were similar for each group. Cox hazard analyses also identified that splenectomy is a protective factor for DFS. The DFS rates in patients who underwent splenectomy, either splenectomy before hepatectomy or synchronous splenectomy and hepatectomy, were significantly higher than those of patients who underwent hepatectomy alone. Although there was no significant difference in OS rates, a series of studies reported that activated macrophages accumulates in the spleens of tumor-bearing hosts and results in tumor-induced tolerance. As a result, splenectomy could restore lymphocyte function and increase the number of

natural killer cells.^[8,20,21] Previous study reported that combined procedure extended OS after the operation. But in our study, we did not observe such result. Long-term outcomes in a larger cohort should be further investigated.

Laparoscopic surgery was only performed in a small proportion cases of patients in the H-S group and the H-preS group due to the large range of surgery or history of abdominal operation. We found that patients in the synchronous hepatectomy and splenectomy groups had longer operative time and more blood loss, thus resulting in more intraoperative transfusion. Notably, there was no significant difference in postoperative complications between the 3 groups. Most patients in our study received minor hepatectomy due to the risk of postoperative liver failure in the cirrhotic background, which is a troublesome and potentially life-threatening complication. Moreover, preoperative WBC and platelet counts of H-preS group were significantly higher than those of other patients, which increases the success rates of subsequent hepatectomy procedures for treating selected patients with HCC and portal hypertension. Considering that most patients in China have post-hepatitis cirrhosis along with portal hypertension and hypersplenism at the time of consultation, splenectomy could be an alternative option for patients, as it both improves the quality of life and has a higher DFS rate among patients receiving hepatectomy for HCC.

This study had several limitations. First, selection bias may be inherent to the study because it is not a randomized study. To reduce this bias, we selected contemporary case controls in a consecutive manner and excluded patients who received splenectomy after primary hepatectomy. Second, all of these data were collected from only 1 medical center, so the sample size was small. Thirdly, some cases were not thoroughly followed-up due to the insufficient time. Therefore, a randomized control study with a larger sample size is needed to further investigate the role of splenectomy before hepatectomy in improving DFS for patients with HCC and hypersplenism.

In conclusion, our results suggest that no matter splenectomy before hepatectomy or synchronous hepatectomy and splenectomy, hepatectomy with splenectomy may improve DFS rates in patients with HCC and hypersplenism, and splenectomy before hepatectomy alleviates hypersplenism without an increased surgical risk.

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