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Original Article

Improved survival following splenectomy combined with curative treatments for hepatocellular carcinoma in Child B patients: A propensity score matching study

Youliang Pei, Zhanguo Zhang, Abdoul-aziz Mba'nbo-koumpa, Xiaoping Chen and Wanguang Zhang

Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Aims: To explore the benefits of curative treatments (liver resection or local ablation) combined with splenectomy for patients with hepatocellular carcinoma (HCC) and Child grade B liver function.

Methods: We reviewed 245 patients with Child grade B liver function who underwent treatment with curative intent for HCC. Among these patients, 116 patients underwent curative treatment combined with splenectomy (the splenectomy group); the other 129 patients only underwent curative treatment (the non-splenectomy group). A one-to-one matching produced 95 paired patients, perioperative and oncological outcomes were compared, and liver function changes were reassessed 1 year later.

Results: The perioperative liver failure rates were 7.4% and 6.3% ($P = 1.000$) and the 90-day mortality was 4.2% and 6.3% ($P = 0.747$) in the splenectomy group and non-splenectomy group, respectively. The 1-, 3-, and 5-year overall survival rates were remarkably greater in the splenectomy group than in the non-splenectomy group (92.6% vs. 79.8%, 53.4% vs. 34.7%, and 19.9% vs. 11.0%, respectively; $P = 0.004$). In the univariate and multivariate analyses, splenectomy was identified as a protective factor for long-term survival. The proportion of patients whose liver function improved to Child A 1 year after surgery was also higher in the splenectomy group than in the non-splenectomy group (95.4% vs. 83.3%; $P = 0.048$).

Conclusions: Compared with non-splenectomy, curative treatments combined with splenectomy for patients with HCC and Child B grade liver function showed no different perioperative outcomes but achieved significant survival benefit. Splenectomy is a beneficial factor for patients with HCC and Child B liver function; liver function improved significantly 1 year after splenectomy.

Key words: Child B, hepatocellular carcinoma, liver resection, local ablation, splenectomy

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third tumor-related death worldwide and primarily occurs in patients with cirrhotic background.[1] Thus, two potentially lethal diseases coexist in the same patients, and both affect their prognosis.[2] The Child–Pugh–Turcotte (hereinafter referred to as Child) grade, accepted by the most integrated HCC staging system, is a widely used tool to evaluate preoperative liver function.[3] Before selecting the optimal treatment strategy for HCC, it is mandatory to consider not only the tumor burden but also the liver function reserve.[4] Patients with well-preserved liver function (Child A) are potentially eligible for most available treatments, from surgical resection to systemic therapy.[5,6] Decompensated liver function, a robust predictive factor for poor prognosis, is usually defined as Child grade B, precluding most useful treatments other than liver transplantation.[7] According to the HCC treatment guidelines, liver resection is ineligible for patients with decompensated liver

Correspondence: Professor Wanguang Zhang and Professor Xiaoping Chen, Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430030, China.
Email: wgzhang@tjh.tjmu.edu.cn; chenxpchenxp@163.com
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function due to high risk of liver-related morbidity and mortality.[2,5] Theoretically, liver transplantation seems to be the optimal strategy to cure liver tumor and replace the cirrhotic liver for patients with limited tumor burden but decompensated liver function. However, only a small proportion of patients on the transplantation list receive liver transplantation due to the shortage of liver grafts. In recent years, with the improvement of surgical techniques and perioperative care, experienced surgeons can carry out liver resection in selected patients with decompensated liver function,[8–10] even additional aggressive procedures, such as simultaneous splenectomy for hypersplenism or Hassab's operation (pericardial devascularization and splenectomy) for patients with variceal bleeding tendency.[11–15] Several studies had reported that patients with HCC and impaired liver function achieved both short- and long-term survival time after liver resection.[7,8,16,17] For single tumor or multiple small tumors that could not be a candidate for liver resection, local ablation achieved comparable survival outcomes.[18] These surgical treatments (liver resection or local ablation) provide potential curative therapies for patients with HCC and Child grade B liver function that could not undergo liver transplantation.

Child grade B liver function is accompanied by portal hypertension (PH), splenomegaly, coagulopathy, hypoproteinemia, ascites, and poor performance status.[19] Even though tumor recurrence after curative treatments is still the primary cause of death, other subsequent fatal episodes, including the further deterioration of liver function and variceal bleeding, also impact long-term survival.[20] Splenectomy has been regarded as a useful method to prevent variceal bleeding for more than 50 years.[21] Several studies reported that patients with Child B liver function benefited from splenectomy, and liver function in most patients improved significantly 1 year after splenectomy.[22–24] Other studies also indicated that splenectomy combined with hepatectomy could extend disease-free survival and overall survival.[12,15,25] However, these studies had some limitations, with either small sample sizes or heterogeneous populations. In addition, no research has explored the subsequent change in liver function and additional therapy after tumor recurrence. In the present study, we analyzed the short- and long-term outcomes among patients with HCC and Child grade B liver function. To overcome selection bias, we used the propensity score matching (PSM) method to achieve convincing results.

METHODS

BETWEEN JANUARY 2005 and December 2015, 245 patients with HCC and Child grade B liver function underwent curative treatments at the Hepatic Surgery Department of Tongji Hospital (Wuhan, China). To evaluate the effect of splenectomy on the long-term survival and liver function change in Child B patients, these patients were divided into two groups based on the surgical procedures. This study was carried out according to the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of Tongji Hospital.

Preoperative assessment

All patients underwent individual laboratory and radiological tests to evaluate their hepatic reserve and tumor burden. Laboratory tests included liver function test, complete blood count, serum α-fetoprotein (AFP), indocyanine green retention rates at 15 min (ICG R15). The preoperative diagnosis and resectable evaluation of HCC were carried out by ultrasound, contrast-enhanced computed tomography (CT), or magnetic resonance imaging. For patients with decompensated liver function, upper gastroenterological endoscopy was carried out to identify the presence of varices and evaluate its severity. The grade of esophageal varices was classified according to previous reports:[26,27] small, defined as straight varices not disappearing with insufflations; medium, defined as enlarged tortuous, occupying less than one-third of the lumen; and large, defined as coil-shaped, occupying more than one-third of the lumen. The presence of clinically related PH was indirectly defined as the presence of varices and splenomegaly (central thickness of spleen >4 cm) and/or with a platelet count $<100\,000/mm^3$. Liver cirrhosis was assessed on the postoperative specimens by histopathology using the Laennec scoring system and was again classified as mild, moderate, and severe.[28] Usually, mild cirrhosis is defined as most septa thin or one broad septum allowed. Moderate cirrhosis with at least two broad septa, and severe cirrhosis with at least one very broad septum or many minute nodules. If patients had active hepatitis, antiviral therapy was recommended to improve the perioperative safety. Patients with a decompensated liver function would not undergo liver resection until the liver function improved to Child grade A after receiving medical treatment.

Surgical indications for curative treatment and splenectomy

The resectability of the liver tumor was comprehensively assessed, considering both the liver function reserve and tumor burden. Usually, only patients with limited tumor burden but impaired liver function were considered for liver resection. Individual patients with a small tumor located deep in the liver parenchyma or with multiple small tumors that are not suitable for surgical resection should

be considered for local ablation. In general, indications for simultaneous splenectomy are: (i) history of variceal bleeding; (ii) portal hypertension with serum platelet level $<7.5 \times 10^9$/L and white blood cell (WBC) count $<4 \times 10^{12}$/L; and (iii) hypersplenism combined with moderate or large varices.

Surgical procedure

All patients were placed in the supine position, and surgical resections were carried out under general anesthesia by an experienced surgical team. If the liver tumor was located in the right lobe, a bilateral subcostal incision was made for liver resection and splenectomy. If the liver tumor was in the left lobe, a left subcostal incision with upward middle extension was made. Generally, the liver resection was carried out before splenectomy. Intraoperative ultrasound was routinely undertaken to determine the relationship between major hepatic vessels and liver tumors, and it could also detect additional intrahepatic metastasis not found by preoperative radiological tests. The Pringle maneuver was occasionally used in the event of major bleeding. Parenchymal transection was done by the combination of ultrasonic scalpel and bipolar coagulation. Hepatic vessels <2 mm were coagulated with an ultrasound scalpel, whereas larger vascular structures and the intrahepatic bile duct were ligated or clipped. Liver resections were classified into major (more than two segments) and minor (two or fewer segments) according to the Couinaud's classification. In addition, if the preoperative ICG R15 rate was >30%, major hepatectomy was cautiously performed to avoid post-hepatectomy liver failure (PHLF). Anatomical resection was defined as complete removal of Couinaud's segments involved with the tumor, whereas non-anatomical resection included enucleation of the tumor, wedge resection, or limited resection. Local ablation was guided by ultrasound with percutaneous or direct vision before splenectomy. For splenectomy, the splenic artery was ligated first, followed by the splenic vein and the surrounding ligaments. The estimated blood loss and the volume of intraoperative transfusion were both evaluated and recorded carefully by anesthesiologists at the end of surgery for subsequent analysis. The hemostatic fiber was placed on the cut surface and splenic pedicle. The abdominal drainage tubes were routinely placed to collect postoperative fluid accumulation. The resected specimen was sent for histopathological testing.

Postoperative management

After surgery, all patients were delivered to the intensive care unit. If their basic vital signs were stable, these patients were transferred to the general ward. Intravenous antibiotics were used to prevent infectious complications on the first day of surgery. Parenteral nutrition was started immediately after surgery. Patients who underwent splenectomy received anticoagulant therapy with low molecular weight heparin (LMWH, 5 kIU/day) by s.c. injection around the umbilicus tissue on the 3rd day after surgery if no i.p. bleeding was observed. If portal vein thrombosis (PVT) was detected, we doubled the dosage of LMWH (5 kIU/12 h) until its disappearance. For some complicated cases for which LMWH was ineffective, warfarin or urokinase were given to promote dissolution of the PVT. Liver function, coagulation function, and blood cell count were routinely measured at 1, 3, 5, and 7 days after surgery. The therapeutic strategy was adjusted based on these tests. If the drainage volume wa less than 150 mL/day and no bile leakage or abdominal infection was detected, the drainage tubes were removed. The Clavien–Dindo classification categorized the postoperative complications and grade III, IV, and V complications were defined as "major" complications.[29] Post-hepatectomy liver failure was defined by the "50–50 criteria", which is a combination of prothrombin time index <50% and serum total bilirubin levels >50 μmol/L on postoperative day 5.[30]

Follow-up

For patients who underwent splenectomy, anticoagulation therapy with LMWH by daily s.c. injection, to prevent the development of PVT, lasted for 3 months after discharge. Antiviral treatment continued until serum virology was completely clear. All patients were investigated with liver function tests, serum AFP level, and abdominal ultrasound or contrast-enhanced CT scan every 3 months during the 2 years after surgery; after which, the interval would extend to every 6 months. The liver function change 1 year after the operation was recorded and compared with the preoperative counterpart. Tumor recurrence was defined as new lesions detected by radiological test with or without increasing levels of serum AFP. The decision to treat recurrent tumors was based on the tumor burden and liver function reserve. Subsequent resection, local ablation, liver transplantation, or transarterial chemoembolization was assigned accordingly.

Statistic analysis and PSM

One-to-one matching using the PSM method was undertaken to overcome potential selection bias between the two groups. The PSM model was generated using possible covariables that could affect the group allocation. The following covariates were matched: age, sex, hepatitis profile, comorbidity, variceal status, liver function, prothrombin time, WBC and platelet count, AFP level,

cirrhosis, Child score, ICG R15, tumor size, and tumor number. The PSM model was generated using the PSM program through the SPSS R-Plugin (https://developer.ibm.com/predictiveanalytics/downloads/), which utilized a newly written R code. The analysis applied single nearest-neighbor matching, without replacement (a single participant could not be selected multiple times). Normally distributed continuous variables were expressed as mean ± standard deviation, whereas continuous variables with a non-normal distribution were expressed as the median with interquartile range (IQR). Differences between groups were compared using the Mann–Whitney *U*-test and Wilcoxon's rank test before and after matching. Categorical variables were reported as the number of cases and prevalence was analyzed by the χ^2-test with the Yates correction or Fisher's exact test, as appropriate. Patients' survival curves were computed using the Kaplan–Meier method and compared using the log–rank test. Disease-free survival (DFS) was measured from the date of operation until the detection of tumor recurrence. Overall survival (OS) was defined as the interval between the date of operation and the date of tumor-related death; patients who died from other causes were defined as censored. Factors influencing OS were analyzed using multivariate analysis with Cox's proportional hazard model. We used two-sided *P*-values of <0.05. $P < 0.05$ was considered statistically significant. All statistical analyses were undertaken with SPSS version 24.0 (IBM, Armonk, NY, USA).

RESULTS

DURING THE STUDY period, a total of 245 patients with HCC and Child grade B liver function who underwent curative treatment (liver resection or local ablation) for HCC were identified. Among these patients, 116 patients underwent splenectomy combined with hepatectomy or local ablation (the splenectomy group), and 129 patients underwent hepatectomy or local ablation alone (the non-splenectomy group). After one-to-one PSM, 95 paired patients were generated. Baseline characteristics of the two groups before PSM are shown in supplemental Table S1. Before PSM, more patients in the splenectomy group had poor performance status. After PSM, no significant difference in baseline variables were noted between the two subgroups, including demographic data, preoperative liver function test, cirrhosis-related portal hypertension, tumor size, and tumor number, except that more patients in the non-splenectomy group had undergone endoscopic therapy before receiving surgical treatment when compared with the splenectomy group (27.4% vs. 7.4%, $P < 0.001$). Due to decompensated liver function, most patients enrolled in the two groups had hypoleukemia, hypothrombinemia, hypoproteinemia, ascites, poor prothrombin time, severe cirrhosis, and large varices. The preoperative characteristics of the two groups are presented in Table 1.

The surgical outcomes and postoperative complications are summarized in Table 2. Most patients in the two groups underwent open liver resection, with only a small proportion of patients undergoing laparoscopic surgery and local ablation. Among patients who received liver resection, only a small portion of patients in this study performed major resection and anatomic resection regarding a high risk of PHLF. In the splenectomy group, 47 patients (49.5%) performed additional pericardial devascularization due to large varices around the esophagus and stomach; no patient undergo this procedure in the non-splenectomy group ($P < 0.001$). Given that additional procedure performed in the splenectomy group, the operating time is longer (257 vs. 185 min; $P < 0.001$) and the intraoperative blood loss is also greater (529 vs. 294 mL; $P < 0.001$) in the splenectomy group when compared with the non-splenectomy group. Fifty-one (53.7%) patients need intraoperative transfusion in the splenectomy group, while only 32 (33.7%) patients need intraoperative transfusion ($P = 0.005$). No patient died during the intraoperative procedures.

Postoperative complications are illustrated in Table 2. Even though more patients in the splenectomy group experienced minor complications when compared with the non-splenectomy group (33.7% vs. 24.2%), no statistical difference was identified ($P = 0.149$); a higher proportion of patients in the splenectomy group experienced major complications (26.3% vs. 14.7%, $P = 0.048$). Respiratory-related complications were significantly high among patients in the splenectomy group, with 21 patients (22.1%), whereas only 8 patients (8.4%) in the non-splenectomy group ($P = 0.014$) experienced respiratory dysfunction. Additionally, patients in the splenectomy group experienced more surgical complications. Postoperative PVT was observed in 30 patients (31.6%), and pancreatic injury in 15 patients (15.8%), whereas no patient in the non-splenectomy group experienced these complications ($P < 0.001$). The postoperative transfusion rate was also higher in the splenectomy group (46.3% vs. 22.1%; $P < 0.001$). In contrast to patients in the non-splenectomy group, more patients had renal dysfunction, perioperative variceal bleeding, wound infection, intra-abdominal bleeding in the splenectomy group, but no statistical difference was found. Liver-related complications, reoperation rate, and 90-day mortality were similar between the two groups. Seven patients (7.4%) in the

Table 1 Baseline characteristics of Child B patients with hepatocellular carcinoma who underwent splenectomy and curative treatment (splenectomy group) or curative treatment alone (non-splenectomy group), after propensity score matching

Variable	Splenectomy group ($n = 95$)	Non-splenectomy group ($n = 95$)	*P*-value
Age, years	51.98 ± 11.13	51.77 ± 8.72	0.885
Gender			
Male	82 (86.3)	81 (85.3)	1.000
Female	13 (13.7)	14 (14.7)	
Comorbidity			
Hypertension	23 (24.2)	25 (26.3)	0.867
Diabetes mellitus	12 (12.6)	15 (15.8)	0.678
History of variceal bleeding	25 (26.3)	27 (28.4)	0.871
Preoperative endoscopic therapy	7 (7.4)	26 (27.4)	<0.001
Etiology			1.000
HBV infection	89 (93.7)	90 (94.7)	
Others	6 (6.3)	5 (5.3)	
HBV-DNA copy			0.656
Positive	39 (41.1)	36 (37.9)	
Negative	56 (58.9)	59 (62.1)	
BMI, kg/m^2	22.37 ± 2.33	22.28 ± 2.18	0.795
White blood cell count, ×10^{12}/L	3.02 ± 1.58	3.07 ± 0.71	0.779
Platelet count, ×10^9/L	48.80 ± 21.58	49.48 ± 12.60	0.791
Albumin, g/L	33.14 ± 4.16	32.83 ± 3.61	0.577
Total bilirubin, μmol/L	23.18 ± 12.50	24.70 ± 17.73	0.494
PT, s	16.23 ± 1.57	16.33 ± 1.24	0.611
AFP, ng/mL			0.461
Positive	59 (62.1)	53 (55.8)	
Negative	36 (37.9)	42 (44.2)	
Cirrhosis†			0.437
Mild	5 (5.3)	7 (7.4)	
Medium	25 (26.3)	18 (18.9)	
Severe	65 (68.4)	70 (73.7)	
Esophageal varices‡			0.479
Small	25 (26.3)	22 (23.2)	
Median	21 (22.1)	16 (16.8)	
Large	49 (51.6)	57 (60)	
Presence of ascites	78 (82.1)	75 (78.9)	0.714
Child score			0.860
7	72 (75.8)	69 (72.6)	
8	20 (21.1)	22 (23.2)	
9	3 (3.2)	4 (4.2)	
MELD score	9.1 ± 1.7	9.4 ± 1.4	0.782
ICG R15, %	28.4 ± 10.0	28.0 ± 7.5	0.794
ASA score			1.000
>2	87 (91.6)	87 (91.6)	
≤2	8 (8.4)	8 (8.4)	
ECOG score			0.866
0	73 (76.8)	71 (74.7)	
1	22 (23.2)	24 (25.3)	
Spleen thickness, cm	5.43 ± 0.92	5.38 ± 0.49	0.658
Portal vein diameter, cm	1.35 ± 0.19	1.34 ± 0.13	0.600
Median tumor size, cm	3.43 ± 1.55	3.42 ± 1.20	0.954
Largest tumor size, cm			0.885
>3	47 (49.5)	46 (48.4)	
≤3	48 (50.5)	49 (51.6)	
Tumor number			1.000
Solitary	88 (92.6)	87 (91.6)	
Multiple	7 (7.4)	8 (8.4)	

(*Continues*)

Table 1. (Continued)

Data are expressed as *n* (%) or mean ± standard deviation.
†Cirrhosis was graded using the following criteria: mild, most septa thin, one broad septum allowed; moderate, at least two broad septa; and severe, at least one very broad septum or many minute nodules.
‡Grade of varices were classified as: small, straight varices not disappearing with insufflations; medium, enlarged tortuous, occupying <1/3 of lumen; and large, coil-shaped, occupying >1/3 of lumen.
AFP, α-fetoprotein; ASA, American Society of Anesthesiologists; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; ICG R15, indocyanine green retention rate at 15 min; MELD, Model for End-stage Liver Disease; PT, prothrombin time.

splenectomy group and six patients (6.3%) in the non-splenectomy group ($P = 1.000$) developed transient PHLF due to poor liver function reserve. Three patients required reoperation due to uncontrolled intra-abdominal bleeding, two (2.1%) in the splenectomy group and one (1.1%) in the non-splenectomy group ($P = 1.000$). Ten patients died within 90 days after surgery: four patients (4.2%) in the splenectomy group (two from tumor recurrence and two from liver failure) and six patients (6.3%) in the non-splenectomy group (three from tumor recurrence, two from liver failure, and one from variceal bleeding) ($P = 0.747$).

Follow-up information and long-term outcomes are summarized in Table 3. The median follow-up time was 42 months (IQR, 33–51) in the splenectomy group and 38 months (IQR, 29–44) in the non-splenectomy group. During the follow-up period, even though there was no

Table 2 Comparision of surgical outcomes and postoperative complications between Child B patients with hepatocellular carcinoma who received splenectomy and curative treatment (splenectomy group) or curative treatment alone (non-splenectomy group)

Variable	Splenectomy group	Non-splenectomy group	*P*-value
Surgical procedure			0.678
Laparoscopic surgery	12 (12.6)	15 (15.8)	
Open surgery	83 (87.4)	80 (84.2)	
Surgical manner			0.637
Liver resection	68 (71.6)	64 (67.4)	
Local ablation	27 (28.4)	31 (32.6)	
Pericardial devascularization	47 (49.5)	0 (0.0)	<0.001
Anatomic resection	9 (9.5)	12 (12.6)	0.644
Major hepatectomy	3 (3.2)	5 (5.3)	0.721
Operative time, min	257 ± 71	185 ± 86	<0.001
Estimated blood loss, mL	529 ± 479	294 ± 311	<0.001
Intraoperative blood transfusion	51 (53.7)	32 (33.7)	0.005
Intraoperative mortality	0 (0.0)	0 (0.0)	N/A
Total complications			
Minor	32 (33.7)	23 (24.2)	0.149
Major	25 (26.3)	14 (14.7)	0.048
General complication			
Respiratory	21 (22.1)	8 (8.4)	0.014
Renal	4 (4.2)	0 (0.0)	0.121
Variceal hemorrhage	3 (3.2)	1 (1.1)	0.621
Surgical complication			
Wound infection	6 (6.3)	2 (2.1)	0.279
Intra-abdominal bleeding	3 (3.2)	2 (2.1)	1.000
PVT	30 (31.6)	0 (0.0)	<0.001
Pancreatic injury	15 (15.8)	0 (0.0)	<0.001
Postoperative transfusion	44 (46.3)	21 (22.1)	<0.001
Liver-related			
Bile leakage	3 (3.2)	1 (1.1)	0.621
Transient PHLF	7 (7.4)	6 (6.3)	1.000
Reoperation	2 (2.1)	1 (1.1)	1.000
Length of hospital stay, days	18.2 ± 7.0	16.4 ± 5.5	0.069
90-day mortality	4 (4.2)	6 (6.3)	0.747
Tumor recurrence	2 (2.1)	3 (3.2)	
Liver failure	2 (2.1)	2 (2.1)	
Variceal bleeding	0 (0.0)	1 (1.1)	

Data are expressed as *n* (%) or mean ± standard deviation.
N/A, not available; PHLF, post-hepatectomy liver failure; PVT, portal vein thrombosis.

Table 3 Follow-up information and long-term outcomes among Child B patients with hepatocellular carcinoma who received splenectomy and curative treatment (splenectomy group) or curative treatment alone (non-splenectomy group)

Variable	Splenectomy group, *n* (%)	Non-splenectomy group, *n* (%)	*P*-value
Median follow-up period, months	42 (33–51)	38 (29–44)	0.673
Death	80 (84.2)	76 (80.0)	0.571
Recurrence	79 (83.2)	89 (93.7)	0.039
Time to recurrence			<0.001
<2 years	43 (54.4)	73 (82.0)	
≥2 years	36 (45.6)	16 (18.0)	
Recurrence pattern			0.014
Intrahepatic	78 (82.1)	81 (85.3)	
Extrahepatic	0 (0.0)	5 (5.3)	
Both	1 (1.1)	3 (3.2)	
Recurrence treatment			0.004
Reoperation	4 (5.1)	1 (1.1)	
TACE	32 (40.5)	18 (20.2)	
Local ablation	18 (22.8)	11 (12.6)	
Transplantation	1 (1.3)	5 (5.6)	
Best support	32 (40.5)	48 (53.9)	
Experience of variceal bleeding	5 (5.3)	14 (14.7)	0.047
Cause of death			0.006
Tumor recurrence	75 (93.8)	58 (76.3)	
Liver failure	3 (3.8)	12 (15.8)	
Variceal bleeding	1 (1.3)	6 (7.9)	
Other reasons	1 (1.3)	0 (0.0)	
Liver function 1 year after surgery			0.024
Child grade A	75 (94.9)	55 (83.3)	
Child grade B	4 (5.1)	11 (16.7)	

TACE, transcatheter arterial chemoembolization.

significant difference in the number of deaths between the groups, a statistical difference was found in time to recurrence, pattern of recurrence, subsequent treatments, the experience of variceal rebleeding, the cause of death, and liver function change within 1 year after surgery (both $P < 0.05$). In the non-splenectomy group, more patients experienced tumor recurrence, recurrence within 2 years, extrahepatic metastasis, presence of variceal rebleeding, and death from liver failure and variceal rebleeding. While in the splenectomy, more patients experienced tumor recurrence beyond 2 years, more patients received reoperation, transcatheter arterial chemoembolization (TACE), and local ablation; most patients died from tumor

recurrence. In contrast to patients in the non-splenectomy group, more patients in the splenectomy group had Child grade A liver function 1 year after surgery (94.9% vs. 83.3%, $P = 0.024$). Long-term survival outcomes were also statistically different between the two groups regarding DFS and OS. The 1-, 3-, and 5-year DFS rates were 83.2%, 28.0%, and 0.0% in the splenectomy group, and were 65.5%, 9.7%, and 0.0% in the non-splenectomy group ($P < 0.001$) (Fig. 1). The 1-, 3-, and 5-year OS rates were longer in the splenectomy group than in the non-splenectomy group (92.6% vs.79.8%, 53.4% vs. 34.7%, and 19.9% vs. 11.0%, respectively; $P = 0.004$) (Fig. 2).

In univariate Cox hazard analysis, Child score 8 (hazard ratio [HR], 0.406; 95% confidence interval [CI], 0.179–0.920; $P = 0.031$), Child score 9 (HR, 0.304; 95% CI, 0.140–0.656; $P = 0.002$), ECOG score more than 0 point (HR, 1.933; 95% CI, 1.087–3.438; $P = 0.025$), splenectomy (HR, 0.633; 95% CI, 0.459–0.873; $P = 0.005$), tumor size >3 cm (HR, 1.663; 95% CI, 1.205–2.294; $P = 0.002$), multiple tumors (HR, 5.585; 95% CI, 3.994–8.591; $P < 0.001$), and postoperative liver failure (HR, 2.190; 95% CI, 1.181–4.058; $P = 0.013$) were significant factors correlated with OS. Furthermore, Child score 8 (HR, 0.348; 95% CI, 0.149–0.813; $P = 0.015$), Child score 9 (HR, 0.198; 95% CI, 0.087–0.451; $P < 0.001$), ECOG score >0 (HR, 2.452; 95% CI, 1.338–4.492; $P = 0.004$), splenectomy (HR, 0.432; 95% CI, 0.306–0.610; $P < 0.001$), tumor size >3 cm (HR, 1.284; 95% CI, 0.870–1.896; $P = 0.029$), multiple tumor (HR, 6.875; 95% CI, 4.254–11.111; $P < 0.001$), and postoperative liver failure (HR, 2.627; 95% CI,1.351–5.109; $P = 0.004$) remained survival prognosticators in multivariate analysis. Splenectomy was identified as a significant protective factor for long-term survival (Table 4).

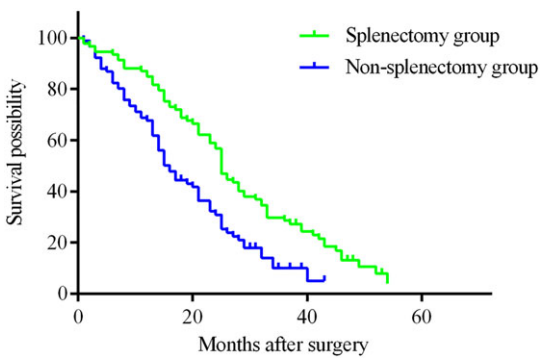

Figure 1 Disease-free survival (DFS) in Child B patients with hepatocellular carcinoma who underwent splenectomy and liver resection or local ablation (splenectomy group) was significantly longer than in those who underwent liver resection or local ablation only (non-splenectomy group). The 1-, 3-, and 5-year DFS rates were 83.2%, 28.0%, and 0.0% in the splenectomy group, and 65.5%, 9.7%, and 0.0% in the non-splenectomy group, respectively ($P < 0.001$). [Color figure can be viewed at wileyonlinelibrary.com]

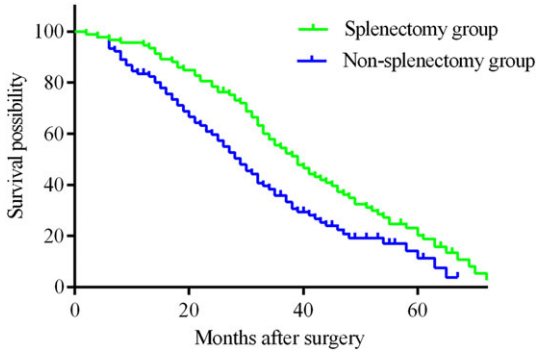

Figure 2 There was a significant difference in overall survival (OS) between Child B patients with hepatocellular carcinoma who underwent splenectomy and liver resection or local ablation (splenectomy group) was significantly longer than in those who underwent liver resection or local ablation only (non-splenectomy group). The 1-, 3-, and 5-year OS rates were longer in the splenectomy group than in the non-splenectomy group (92.6% vs.79.8%, 53.4% vs. 34.7%, and 19.9% vs. 11.0%, respectively; $P = 0.004$). [Color figure can be viewed at wileyonlinelibrary.com]

One year after surgery, we successfully tested liver function in 145 patients, 79 patients in the splenectomy group and 66 patients in the non-splenectomy group. The liver function changes of 66 newly paired patients were reassessed. Table 5 shows the comparison of liver function change between the two groups. In contrast to patients in the non-splenectomy group, white blood cell count and platelet count in the splenectomy group was significantly elevated, and aspartate transaminase, total bilirubin, prothrombin time, and Child score decreased remarkably ($P < 0.001$). More patients with preoperative Child grade B liver function improved to Child grade A after splenectomy. Albumin levels in the non-splenectomy group were also significantly elevated, but the elevation was greater in the splenectomy group.

DISCUSSION

LIVER TRANSPLANTATION IS the optimal treatment option for patients with limited tumor burden and Child grade B liver function. However, the number of patients on the transplantation list is greater than the number

Table 4 Univariate and multivariate analyses of prognostic factors for overall survival among Child B patients with hepatocellular carcinoma who received splenectomy and curative treatment, or curative treatment alone, using the Cox hazard model

Variables	Univariate analysis HR (95% CI)	*P*-value	Multivariate analysis HR (95% CI)	*P*-value
History of variceal bleeding (yes vs. no)	1.013 (0.704–1.458)	0.944		
Endoscopic therapy (yes vs. no)	0.934 (0.599–1.458)	0.763		
Child score				
7 vs. 8	0.406 (0.179–0.920)	0.031	0.348 (0.149–0.813)	0.015
7 vs. 9	0.304 (0.140–0.656)	0.002	0.198 (0.087–0.451)	<0.001
Cirrhosis				
Mild vs. severe	0.477 (0.222–1.026)	0.058	0.454 (0.197–1.044)	0.063
Mild vs. medium	1.072 (0.738–1.556)	0.716	1.295 (0.862–1.945)	0.213
Varices				
Small vs. large	0.671 (0.441–1.021)	0.063	0.956 (0.610–1.499)	0.845
Small vs. medium	0.770 (0.526–1.128)	0.179	1.317 (0.851–2.040)	0.217
ASA score (≤2 vs. >2)	1.082 (0.585–2.001)	0.804		
ECOG score (0 vs. 1)	1.933 (1.087–3.438)	0.025	2.452 (1.338–4.492)	0.004
Pericardial devascularization (yes vs. no)	0.888 (0.620–1.272)	0.517		
Splenectomy (yes vs. no)	0.633 (0.459–0.873)	0.005	0.432 (0.306–0.610)	<0.001
Presence of ascites (yes vs. no)	1.096 (0.731–1.096)	0.658		
Therapeutic manner (Resection vs. ablation)	1.061 (0.758–1.484)	0.730		
Intraoperative transfusion (yes vs. no)	0.881 (0.637–1.218)	0.442		
Tumor diameter (>3 cm vs. ≤3 cm)	1.663 (1.205–2.294)	0.002	1.284 (0.870–1.896)	0.029
Tumor number (multiple vs. solitary)	5.858 (3.994–8.591)	<0.001	6.875 (4.254–11.111)	<0.001
HBV-DNA copy (positive vs. negative)	1.093 (0.790–1.512)	0.593		
AFP level (negative vs. positive)	0.935 (0.678–1.289)	0.680		
Postoperative liver failure (yes vs. no)	2.190 (1.181–4.058)	0.013	2.627 (1.351–5.109)	0.004

AFP, α-fetoprotein; ASA, American Society of Anesthesiologists; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HR, hazard ratio.

of potential organ donors, making it essential to adopt alternative treatments for these patients, even if these options are inferior to liver transplantation. Our study, not the first attempt, provided a challenging alternative that some selective HCC patients with decompensated liver function could benefit from simultaneous splenectomy and curative treatments. The DFS and OS rates in splenectomy patients were significantly higher than in patients who underwent liver resection or local ablation alone, and liver function in most patients improved 1 year after splenectomy. The postoperative complications in our study are relatively high compared with other studies, but the lethal comorbidity is acceptable. We suggest that simultaneous splenectomy combined with liver resection or local ablation are safe and beneficial for some selected HCC patients with Child grade B liver function.

Patients with decompensated liver function usually experience portal hypertension, hypersplenism, and thrombocytopenia, which could cause decreases in WBC and platelet counts and coagulopathy, precluding subsequent curative treatment for HCC.[7] Unlike most countries in Europe and North America, where HCC and hepatic decompensation is regarded as a contradiction to surgical resection,[2,31] liver resection or local ablation combined with other aggressive surgical procedures, such as splenectomy with or without Hassab's operation, are still carried out in some Asian countries, mainly due to the lack of liver donors and no better alternatives.[13,14,32–34] Splenectomy alone has been reported as a useful measure to extend the surgical indication, as this procedure could improve the liver function within a short time.[22,33] In the past, some surgeons thought that, for patients with HCC complicated with the decompensated liver function, splenectomy should be carried out first, then hepatectomy after the improvement of liver function.[35] This two-stage splenectomy and hepatectomy was used to decrease the high risk of bleeding with liver resection and postoperative complications, whereas repeated abdominal surgery within a short time also increased the risk of other complications and inevitably prolonged the treatment period.

Table 5 Comparison of liver function changes at 1 year after surgery in Child B patients with hepatocellular carcinoma who received splenectomy and curative treatment (splenectomy group) or curative treatment alone (non-splenectomy group)

	Before surgery	One year after surgery	*P*-value
Splenectomy group ($n = 66$)			
White blood cell count, $\times 10^{12}$/L	2.84 ± 1.26	6.15 ± 1.15	<0.001
Platelet count, $\times 10^{9}$/L	45.2 ± 19.8	155.3 ± 33.9	<0.001
Aspartate transaminase, U/L	45.0 ± 25.1	31.3 ± 21.8	<0.001
Total bilirubin, μmol/L	22.5 ± 9.2	18.6 ± 4.4	<0.001
Albumin, g/L	33.2 ± 3.8	41.8 ± 3.9	<0.001
Prothrombin time, s	16.3 ± 1.4	12.9 ± 1.1	<0.001
Presence of ascites	60 (90.9)	3 (4.6)	<0.001
Child score	7.2 ± 0.4	5.2 ± 0.5	<0.001
Child grade A	0 (0.0)	63 (95.4)	<0.001
Non-splenectomy group ($n = 66$)			
White blood cell count, $\times 10^{12}$/L	3.22 ± 0.65	3.38 ± 0.47	0.091
Platelet count, $\times 10^{9}$/L	50.7 ± 13.4	52.4 ± 13.0	0.523
Aspartate transaminase, U/L	42.5 ± 17.7	31.3 ± 11.5	<0.001
Total bilirubin, μmol/L	23.8 ± 15.4	20.1 ± 3.0	0.070
Albumin, g/L	33.1 ± 3.8	37.6 ± 3.6	<0.001
Prothrombin time, s	16.3 ± 1.2	12.8 ± 1.5	<0.001
Presence of ascites	62 (93.9)	11 (16.7)	<0.001
Child score	7.3 ± 0.5	5.4 ± 0.8	<0.001
Child grade A	0 (0.0)	55 (83.3)	<0.001

Data are expressed as *n* (%) or mean ± standard deviation.

The recent improvements in preoperative evaluation, postoperative care, and minimally invasive surgery have made it feasible to undertake surgical resection in some selected patients with Child grade B liver function.[10,36] For small liver tumors located deep in the liver parenchyma or the center of the liver, local ablation provides an alternative curative treatment option, achieving comparable oncological outcomes but remarkable low complication rates.[18] Some patients with small tumors located on the peripheral surface of the liver are also recommended for liver resection instead of local ablation. In the present study, most patients underwent liver resection, except for some patients with tumor size <3 cm and multiple tumors that were not considered candidates for liver resection.

Decompensated liver function and the presence of large varices are usually considered as contraindications for liver resection due to a high risk of perioperative mortality and PHLF rates.[7] Most of the patients enrolled in our study had severe cirrhosis and large varices, half of whom underwent additional splenectomy. Even though endoscopic therapy (sclerotherapy or band ligation) and transjugular intrahepatic portosystemic shunt are the standard treatments for variceal patients in Europe and North America,[20] splenectomy combined with or without Hassab's procedure is more common in our center. Unsurprisingly, the proportion of postoperative complications was relatively high, but fatal complications were similar to that in other studies. A recent meta-analysis concluded that there is no difference in terms of perioperative mortality and PHLF between simultaneous surgery and liver resection alone for patients with HCC and PH.[15] Major complications in the two groups are also comparable in our study.

The specific mechanism of improvement of liver function after splenectomy is still unknown. Several studies have found that splenectomy could improve liver function among patients with Child grade B liver function.[22,24,37] In our research, hepatic function in most patients was ameliorated 1 year after surgery, especially among patients who underwent splenectomy. One possible factor contributes this effect is that these patients received additional medical treatments or changed their lifestyles, such as antiviral therapy, smoking cessation, and alcohol withdrawal. Other potential beneficial factors could be the increased platelet count after splenectomy. It has been reported that platelets play a vital role in liver regeneration after partial hepatectomy in animal models.[38,39] The rapidly elevated platelet count after splenectomy could promote liver regeneration, which is beneficial to the recovery of liver function. Platelets can also delay fibrosis of chronic

intoxication in an animal model.[40,41] The difference in liver function improvement between the two groups makes us believe that splenectomy can significantly improve the liver function of Child grade B patients.

The possible reasons for the combined procedure contributing to prolonged DFS and OS after the operation are as follows. First, the increased platelet count and improvement of liver function improved the quality of life, making it feasible to receive available treatments after tumor recurrence. Second, splenectomy or Hassab's operation could decrease the portal inflow, reducing episodes of variceal bleeding, as well as mortality from non-tumorigenic causes. Furthermore, a series of studies reported that splenectomy could promote the antitumor effect through restoring lymphocyte function,[42] increasing the number of natural killer cells,[35,43] and decreasing myeloid-derived suppressor cells *in vivo*.[44] However, compared with patients without splenectomy, patients receiving splenectomy had a longer overall survival. In terms of the limited tumor burden in our study, survival time is not satisfactory in either group, and most patients died from tumor recurrence, suggesting that the cirrhosis background could not be reversed to normal even if the liver function of most patients was significantly improved after splenectomy. Moreover, liver resection or local ablation is the only strategy to achieve a potentially curative treatment when compared with other therapeutic options like TACE or sorafenib if liver transplantation is unavailable.[2] In addition, univariate and multivariate Cox hazard analyses both identified that splenectomy is a protective factor for long-term survival in Child B patients with HCC. Considering that China is the biggest developing country and accounts for almost half of all HCC patients worldwide, any non-transplantation attempt that could achieve improved long-term survival should be encouraged. Liver resection or local ablation combined with splenectomy could be an alternative, but not the perfect, option for patients with limited tumor burden and decompensated liver function if economic factors and subsequent unavailability of liver transplantation were considered.

Several limitations of this study should be mentioned. First, although the PSM analysis is applied in this study, potential selection bias still exists. Second, the sample size is relatively small and originates from a single center. A prospective randomized control trial is required to identify the real role of splenectomy in decompensated HCC patients to overcome these shortcomings. In addition, the liver function changes in this study were followed up in 1 year after surgery due to the inconsistency of follow-up compliance in the same center. Long-term outcomes of liver function and immunobiological changes should be further followed and investigated. Also, the primary etiology in our study is HBV infection; whether patients with liver cirrhosis caused by other etiology can benefit from simultaneous splenectomy is still unknown. Furthermore, most patients who were candidates for liver transplantation underwent alternative treatments in this study, and the actual survival gap between liver transplantation and alternative therapy is still unknown. Considering the survival difference in our research, future researchers focusing on these decompensated HCC patients should compare the long-term outcomes of this surgical procedure to liver transplantation and identify those who can benefit the most from simultaneous splenectomy and liver resection or local ablation.

In conclusion, hepatectomy or local ablation combined with splenectomy can be safely carried out in some selected patients with HCC and Child grade B liver function. The combined procedure shows acceptable mortality and major complications, and favorable survival benefit. Simultaneous splenectomy achieved improved OS time and provided a higher proportion of Child grade B liver function conversion to Child grade A 1 year after splenectomy.

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SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found online in the Supporting Information section at the end of the article.

Table S1 Baseline characteristics of each treatment subgroup before propensity score matching.