ORIGINAL ARTICLE

Influence of Child–Pugh B7 and B8/9 cirrhosis on laparoscopic liver resection for hepatocellular carcinoma: a retrospective cohort study

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Abstract

Background Laparoscopic liver resection for hepatocellular carcinoma (HCC) in patients with Child–Pugh A cirrhosis has been shown to be beneficial. However, less is known regarding the outcomes of such treatment in patients with Child–Pugh B cirrhosis. We conducted a retrospective study to evaluate the outcomes of laparoscopic liver resection for HCC in patients with Child–Pugh B cirrhosis, focusing on surgical risks, recurrence, and survival.

Methods 357 patients with HCC who underwent laparoscopic liver resection from 2007 to 2021 were identified from our single-institute database. The patients were divided into three groups by their Child–Pugh score: the Child–Pugh A ($n = 280$), Child–Pugh B7 ($n = 42$), and Child–Pugh B8/9 groups ($n = 35$). Multivariable Cox regression models for recurrence-free survival (RFS) and overall survival (OS) were constructed with adjustment for preoperative and postoperative clinicopathological factors.

Results The Child–Pugh B8/9 group had a significantly higher complication rate, but the complication rates were comparable between the Child–Pugh B7 and Child–Pugh A groups (Child–Pugh A vs. B7 vs. B8/9: 8.2% vs. 9.6% vs. 26%, respectively; $P = 0.010$). Compared with the Child–Pugh A group, the risk-adjusted hazard ratios (95% confidence intervals) in the Child–Pugh B7 and B8/9 groups for RFS were 1.39 (0.77–2.50) and 3.15 (1.87–5.31), respectively, and those for OS were 0.60 (0.21–1.73) and 1.80 (0.86–3.74), respectively. There were no significant differences in major morbidities (Clavien–Dindo grade > II) ($P = 0.117$) or the proportion of retreatment after HCC recurrence ($P = 0.367$) among the three groups.

Conclusion Among patients with HCC, those with Child–Pugh A and B7 cirrhosis can be good candidates for laparoscopic liver resection in terms of complications and recurrence. Despite poor postoperative outcomes in patients with Child–Pugh B8/9 cirrhosis, laparoscopic liver resection is less likely to interfere with retreatment and can be performed as part of multidisciplinary treatment.

Graphical abstract
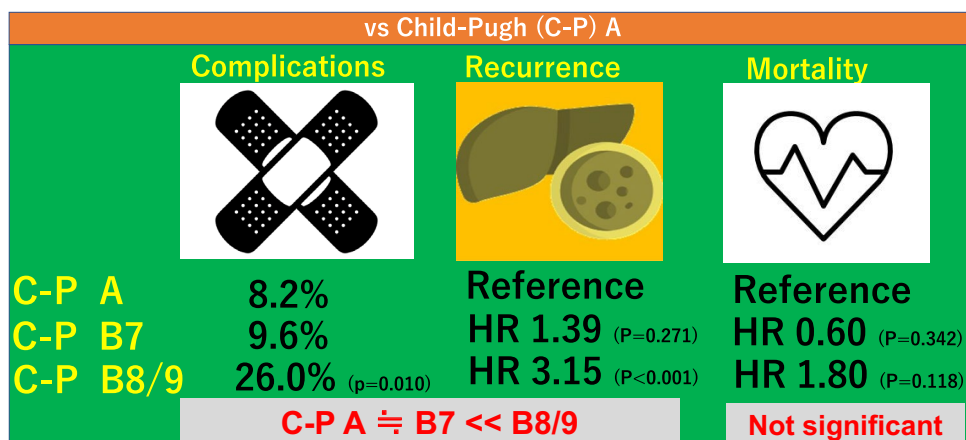
Extended author information available on the last page of the article

Hepatocellular carcinoma (HCC) is the most common primary liver tumor and one of the leading causes of cancer-related death worldwide [1, 2]. HCC occurs primarily in patients with underlying liver disease, which negatively affects the prognosis and increases the complexity of treatment [3, 4]. Patients are offered surgical treatment, such as liver resection or transplantation, as well as other types of treatment: percutaneous ablation [5], transarterial chemoembolization (TACE), or chemotherapy [6, 7]. Candidacy for surgical resection is dictated by the severity of the patient's underlying liver dysfunction and the degree of resection that wound be mandated by the size and number of tumors. Surgical options such as liver transplantation and resection represent the treatments of choice because they offer long-term survival [8, 9]. The Child–Pugh classification has been proposed as a scoring system to grade liver function and is currently adopted by most of the available guidelines on HCC treatment [10–13].

In the Barcelona Clinic Liver Cancer algorithm, which has been advocated by most researchers as the optimal staging system for prognosis prediction and treatment of HCC, only patients with early-stage tumors may be considered for liver resection because resection of such tumors is associated with long-term survival [7, 14]. Furthermore, preserved liver function (Child–Pugh A cirrhosis without ascites) is considered a necessary condition to obtain optimal outcomes after liver resection [6]. Conversely, it is generally agreed that in the setting of Child–Pugh C cirrhosis, patients without significant risk factors should be listed for transplantation according to well-defined inclusion criteria [15]. However, no clear recommendations for treatment of HCC in patients with Child–Pugh B cirrhosis have been established. Treatment allocation remains difficult and controversial because these patients have an intermediate, partially compromised situation between well-preserved and terminal liver function [16–18]. Liver transplantation is an optimal and definitive treatment because it eliminates the malignancy while restoring normal liver function; however, it is offered only to select patients who fulfill specific criteria, and organ availability is scarce worldwide, limiting the application of this option. Locoregional therapies and systematic chemotherapy are mainly adopted for patients who cannot undergo liver transplantation or resection. In such conditions, however, survival outcomes are reportedly worse than those of curative treatments; additionally, the risk of collateral liver damage is still unclear, with some reports disclosing a high likelihood of decompensation [6, 16, 17].

Laparoscopic surgery can be a reasonable option in many patients because it minimizes surgical stress and enhances patient recovery [19]. Laparoscopic liver resection (LLR) is gaining popularity as a treatment for HCC, being associated with better short-term outcomes and similar oncological survival to the standard open approach [20–23]. Additionally, some series have demonstrated that LLR provides acceptable outcomes in both patients with and without cirrhosis [24, 25]. However, most patients included in studies performed to date had early Child–Pugh A cirrhosis, and the role of laparoscopy in the setting of more advanced cirrhosis remains uncertain [26]. By clarifying the results of LLR for patients with Child–Pugh B cirrhosis, we may be able to overcome limitations previously thought to be insurmountable and offer a safer surgical approach for patients with more advanced cirrhosis.

We hypothesized that LLR, which is considered a minimally invasive surgery, can provide similarly favorable outcomes for patients with Child–Pugh B cirrhosis as for those with Child–Pugh A cirrhosis. This study was performed to compare the short- and long-term outcomes between patients with early (Child–Pugh A) cirrhosis and advanced (Child–Pugh B) cirrhosis undergoing LLR for HCC.

Materials and methods

Patient selection

This retrospective cohort study was performed using a database containing all LLRs performed from January 2007 to December 2021 at Saitama Medical University International Medical Center. The treatment strategy for HCC was determined according to the treatment algorithm of the Japan Society of Hepatology [27]. The inclusion criteria were (a) an age of ≥ 18 years, (b) performance of anatomical or non-anatomical hepatectomy, (c) performance of LLR for HCC, and (d) performance of up to one additional procedure such as ablation or resection. The exclusion criteria were (a) metastatic disease; (b) exploratory laparoscopy and conversion from laparoscopy to laparotomy; (c) main portal vein, hepatic artery, biliary duct, or inferior vena cava invasion requiring major reconstruction; (d) Child–Pugh C cirrhosis; and (e) associated extrahepatic resection.

We extracted the following clinical and pathological data from the database: age, sex, body mass index (BMI), American Society of Anesthesiologists performance score, hypertension, diabetes, hepatitis B/C infection, clinical

cancer stage according to the tumor-node-metastasis (TNM) Classification of Malignant Tumors (Union for International Cancer Control, 8th edition) [28], Model for End-Stage Liver Disease (MELD) score [29], clinical staging according to albumin–bilirubin (ALBI) score [30] and the Japan Integrated Staging (JIS) score [31], previous treatment, ascites within 30 days prior to surgery, laboratory values, Child–Pugh grade, indocyanine green (ICG) retention rate, type of resection (i.e., anatomical or non-anatomical), LLR difficulty score in the IWATE criteria [32], intraoperative data (blood loss, transfusions, and operation time), short-term outcomes (90-day morbidity, major morbidity, complications, and postoperative hospital stay), tumor size and grade, pathologic data [microvascular invasion, capsular invasion, and margin status (i.e., R0 or R1)], and oncological outcomes [recurrence, treatment of recurrence, recurrence-free survival (RFS), and overall survival (OS)]. Informed consent was obtained in accordance with the principles of the Declaration of Helsinki. Data regarding the patients and their complications were extracted from our institution's electronic medical records. This study was approved by the Institutional Review Board of Saitama Medical University International Medical Center (No. 19-313). The STROBE guidelines were followed [33].

Child–Pugh grade

Most previous studies analyzed the association of short-term outcomes with the Child–Pugh grade [26, 34–36]. According to early studies, we divided all patients with liver cirrhosis into the following two groups: the early cirrhotic group, consisting of patients with Child–Pugh A cirrhosis, and the advanced cirrhotic group, consisting of patients with Child–Pugh B cirrhosis. We then created three categories by dividing the advanced cirrhotic group into the following two groups: the Child–Pugh B7 group (Child–Pugh score of 7) and the Child–Pugh B8/9 group (Child–Pugh score of 8 or 9).

Outcomes of interest

The patients were followed up for recurrence by measurement of serum tumor markers and imaging, including ultrasonography, computed tomography, and magnetic resonance imaging. We followed up the patients once every 3 months for the first 3 years and then every 6 months thereafter.

The primary endpoint was evaluation of the long-term oncological outcomes, measured as RFS and OS. The secondary endpoints were surgical safety, measured as major morbidity (Clavien–Dindo grade > II), and complications [37, 38].

Definitions

Data regarding the patients' characteristics and postoperative course were determined by review of the patients' charts. Portal hypertension was defined as the radiological presence of clinically significant splenomegaly, gastroesophageal varices, umbilical vein recanalization and/or portosystemic shunts, as well as a preoperative platelet count below 100,000/mm^3 [39]. Whenever data on hepatic venous pressure gradient was available, a 10-mmHg cut-off was considered to indicate clinically significant portal hypertension [40]. We measured the ICG retention rate for all patients being considered for liver resection [41]. The tumor size, tumor number, differentiation, microvascular invasion, capsular invasion, and R0 resection were determined based on the results of pathological examinations and in accordance with the General Rules for the Clinical and Pathological Study of Primary Liver Cancer [42]. Tumor size was defined as the size of the largest lesion in patients with multiple nodules. Postoperative complications were graded according to the Clavien–Dindo classification system, with grade I and II complications classified as minor and grade ≥ III classified as major [37, 38]. Postoperative ascites was defined as a drainage output of > 10 mL/kg per 24 h [43]. Posthepatectomy liver failure and bile leakage were defined according to the International Study Group on Liver Surgery [44]. Microvascular invasion was defined as the presence of tumor emboli within the central vein, portal vein, or large capsular vessels or involvement of the segmental or sectional branches of the portal or hepatic veins [45, 46].

Statistical analysis

The chi-square test and Fisher's test were used to analyze categorical data. Postoperative RFS and OS were analyzed using the Kaplan–Meier method, and the log-rank test was used for between-group comparisons. Univariate and multivariate analyses were performed for evaluation of prognostic factors using a Cox regression model. Factors included in the multivariable analysis using the Cox proportional hazard model were also selected on the basis of clinical interest, scientific knowledge, and variables that were identified in previous studies. Inclusion of all variables in the model for OS was not valid because of the limited sample size; therefore, we chose only clinically important parameters: tumor size, tumor number, differentiation, vascular invasion, transfusion, margin status, and Child–Pugh grade.

A P value of < 0.05 was considered statistically significant. All statistical analyses were conducted using STATA statistical software, version 15.0 (StataCorp, College Station, TX).

Results

In total, 565 patients who underwent LLR for HCC at our hospital from January 2007 to December 2021 were identified. Of these 565 patients, 290 had Child–Pugh A cirrhosis and 79 had Child–Pugh B cirrhosis. There were 10 conversions (3.4%) to laparotomy in the Child–Pugh A group: three due to bleeding during parenchymal dissection and seven due to technical difficulty because of adhesions caused by previous liver resections or abdominal surgeries. There were two conversions (4.6%) in the Child–Pugh B7 group: one due to bleeding secondary to portal hypertension, and the other one due to technical difficulty secondary to adhesions caused by previous locoregional therapies. There was no conversion in the Child–Pugh B8/9 group. There was no significant difference in the rate of conversion to laparotomy among the three groups (P = 0.657). The 357 patients who underwent LLR for HCC without conversion were included in the current study.

Table 1 shows the characteristics of the patients in the early cirrhotic group (those with Child–Pugh A cirrhosis) and the advanced cirrhotic group (those with Child–Pugh B cirrhosis). The BMI was significantly lower in the early cirrhotic group than in the advanced cirrhotic group. Variables related to preserved liver function (ALBI score, MELD score, JIS score, prothrombin time, albumin concentration, bilirubin concentration, preoperative encephalopathy, and ICG retention rate) and related to portal hypertension (platelet count and preoperative ascites) were significantly better in the early than advanced cirrhosis group. The proportion of previous treatment, cancer stage, alpha-fetoprotein concentration, and PIVKA-II were not different between the two groups.

Table 2 shows the perioperative outcomes. In the advanced cirrhotic group, the rates of non-anatomical resection (86% vs. 98%, P < 0.001), transfusion (9.3% vs. 42%, P < 0.001), and complications (8.2% vs. 17%, P = 0.033) were significantly higher than those in the early cirrhotic group. However, the difference in major morbidity (Clavien–Dindo grade > II) did not reach statistical significance (3.9% vs. 7.8%, P = 0.221). The difficulty score, operative time, blood loss, postoperative stay, R1 resection, tumor size, differentiation, microvascular invasion, and capsular invasion were comparable between the two groups.

Figure 1 shows the Kaplan–Meier plots for RFS and OS in the early and advanced cirrhotic groups. The 1- and 3-year RFS rates in the early cirrhotic group were 72% and 37%, respectively, and those in the advanced cirrhotic group were 54% and 21%, respectively. The 1- and 3-year OS rates in the early cirrhotic group were 96% and 87%, respectively, and those in the advanced cirrhotic group were 92% and 82%, respectively. The presence of advanced cirrhosis significantly affected RFS (log-rank test, P = 0.003), but it did not contribute to OS (log-rank test, P = 0.30).

Table 3 shows the results of the univariate and multivariate analyses of factors in the Cox regression model for RFS and OS. The univariate analysis showed that age (> 70 years), tumor size (> 2 cm), tumor number, differentiation, microvascular invasion, pre-locoregional therapy, pre-resection, R1 resection, and Child–Pugh grade were significant prognostic factors for RFS (all P < 0.05), while tumor size (> 2 cm) and differentiation were significant prognostic factors for OS. In the multivariate analysis, the factors that were significantly associated with poor RFS were age (> 70 years), tumor number, pre-locoregional therapy, R1 resection, and Child–Pugh grade. In contrast, the significant factors for OS were tumor size (> 2 cm), differentiation, and transfusion. Although patients with advanced cirrhosis were more likely to develop postoperative recurrence than were patients with early cirrhosis [hazard ratio (HR), 2.09; 95% confidence interval (CI), 1.33–3.29; P = 0.001], the difference in OS between the early and advanced cirrhotic groups did not reach statistical significance (HR, 1.17; 95% CI 0.61–2.24; P = 0.646).

Tables 4 and 5 show the patients' characteristics and perioperative outcomes when patients with Child–Pugh B cirrhosis were classified as those with Child–Pugh B7 (n = 42) and B8/9 (n = 35). Among the patients' characteristics, there were significant differences in BMI and variables related to preserved liver function and portal hypertension (Table 4), and among the perioperative outcomes, there were significant differences in non-anatomical resection, transfusion, and complications (Table 5). The Child–Pugh B8/9 group had a higher complication rate than the other two groups (Child–Pugh A vs. B7 vs. B8/9: 8.2% vs. 9.6% vs. 26%, respectively; P = 0.010). The Child–Pugh B8/9 group tended to have higher rates of major morbidities and recurrence than the other two groups, although the differences were not statistically significant (Child–Pugh A vs. B7 vs. B8/9: 3.9% vs. 4.8% vs. 14%, respectively; P = 0.117 and 49% vs. 48% vs. 63%, respectively; P = 0.268).

Figure 2 shows the Kaplan–Meier plots for RFS and OS in each of the three Child–Pugh groups. The 1- and 3-year RFS rates in the Child–Pugh A, B7, and B8/9 groups were 72% and 37%, 62% and 29%, and 44% and 10%, respectively. The 1- and 3-year OS rates in these groups were 96% and 87%, 100% and 86%, and 84% and 77%, respectively. The Child–Pugh grade significantly affected RFS (log-rank test, P < 0.001) and OS (log-rank test, P = 0.03).

Table 6 shows the results of the univariate and multivariate analyses in the Cox regression model among the three Child–Pugh grade groups. In the univariate analysis,

Table 1 Characteristics of patients in Child–Pugh A and B cirrhosis

Characteristic	Child–Pugh grade		
	Child–Pugh A ($n=280$)	Child–Pugh B ($n=77$)	P value
Age, years	71 (65–77)	70 (65–75)	0.506
Sex, male	209 (75)	53 (69)	0.307
BMI, kg/m^2	23.4 ± 3.5	24.9 ± 4.3	0.003*
ASA score			0.479
≤ 2	235 (84)	62 (81)	
> 2	45 (16)	15 (19)	
Hypertension	130 (46)	28 (36)	0.115
Diabetes	93 (33)	24 (31)	0.735
Viral infection, positive	187 (67)	47 (61)	0.347
Cancer stage			0.840
IA–IB	214 (76)	58 (75)	
II–IIIB	66 (24)	19 (25)	
ALBI score			< 0.001*
Grade 1	168 (60)	2 (2.6)	
Grade 2	112 (40)	67 (87)	
Grade 3	0 (0)	8 (10.4)	
MELD score	7 (6–10)	10 (8–12)	< 0.001*
JIS score			< 0.001*
0–1	229 (82)	28 (36)	
2–5	51 (18)	49 (64)	
Previous treatment			
Locoregional therapy	77 (28)	13 (17)	0.057
Resection	46 (16)	7 (9)	0.147
Platelet count, × 10^3/μL	142 ± 61	89 ± 41	< 0.001*
Albumin, g/dL	3.9 (3.7–4.2)	3.3 (3.0–3.4)	< 0.001*
Bilirubin, mg/dL	0.6 (0.5–0.8)	1.1 (0.8–1.5)	< 0.001*
PT, %	89 (80–97)	65 (58–71)	< 0.001*
AFP, ng/mL	7.2 (3.6–28.1)	9.8 (4.1–40.4)	0.249
PIVKA-II, mAU/mL	33 (22–103)	40 (21–117)	0.812
Preoperative ascites	37 (13)	49 (64)	< 0.001*
Preoperative encephalopathy	3 (1)	9 (12)	< 0.001*
Portal hypertension	75 (27)	57 (74)	< 0.001*
ICG retention rate, %	14 (8.1–20.1)	36 (27.6–47.8)	< 0.001*

Data are presented as median (interquartile range), n (%), or mean ± standard deviation

BMI body mass index, *ASA* American Society of Anesthesiologists, *ALBI* albumin-bilirubin, *MELD* Model for End-stage Liver Disease, *JIS* Japan Integrated Staging, *PT* prothrombin time, *AFP* alpha-fetoprotein, *ICG* indocyanine green

*Statistically significant

with reference to the Child–Pugh A group, the HRs (95% CIs) for RFS in the Child–Pugh B7 and Child–Pugh B8/9 groups were 1.22 (0.75–1.97, $P=0.428$) and 2.61 (1.65–4.13, $P<0.001$), respectively. The HRs (95% CIs) for OS in these groups were 0.67 (0.24–1.88, $P=0.450$) and 2.12 (1.12–4.20, $P=0.022$), respectively. The multivariate analysis showed that age (> 70 years), tumor number, pre-locoregional therapy, pre-resection, and Child–Pugh B8/9 cirrhosis were independent significant prognostic factors for RFS. Tumor size (> 2 cm), differentiation, and transfusion were significant prognostic factors for OS. Compared with the Child–Pugh A group, the HRs (95% CIs) for RFS in the Child–Pugh B7 and Child–Pugh B8/9 groups were 1.39 (0.77–2.50, $P=0.271$) and 3.15 (1.87–5.31, $P<0.001$), respectively. The HRs (95% CIs) for OS in these groups were 0.60 (0.21–1.73, $P=0.343$) and 1.80 (0.86–3.74, $P=0.118$), respectively. Child–Pugh B7 cirrhosis was not an independent prognostic factor for RFS and OS. Alternatively, Child–Pugh B8/9 cirrhosis was a significant risk factor for RFS, although not for OS.

Table 2 Perioperative outcomes of patients in Child–Pugh A and B cirrhosis

Characteristic	Child–Pugh grade		
	Child–Pugh A (n = 280)	Child–Pugh B (n = 77)	P value
Position of lesion			0.684
Left	105	31	
Right anterior	77	20	
Right posterior	65	20	
Caudate	8	1	
Multiple	25	5	
Type of hepatectomy			<0.001*
Non-anatomical	240 (86)	76 (98)	
Anatomical	40 (14)	1 (1.3)	
Difficulty score			0.348
Low (1–3)	143 (51)	32 (41)	
Intermediate (4–6)	128 (45)	41 (53)	
Advanced (7–9)	8 (2.9)	4 (5.2)	
Expert (10–12)	1 (0.4)	0	
Operative time, minutes	167 (121–223)	157 (121–209)	0.266
Blood loss, mL	30 (0–100)	35 (0–120)	0.757
Transfusion	26 (9.3)	32 (42)	<0.001*
90-day mortality	1 (0.4)	2 (2.6)	0.119
Major morbidity (Clavien–Dindo grade > II)	11 (3.9)	6 (7.8)	0.221
Complications	23 (8.2)	13 (17)	0.033*
Ascites	7 (2.5)	7 (9.1)	
Liver failure	0 (0)	1 (1.2)	
Bile leakage	3 (1.1)	0 (0)	
Delayed biliary stricture	2 (0.7)	0 (0)	
Abdominal collection	3 (1.1)	1 (1.2)	
Bleeding	2 (0.7)	0 (0)	
ARDS	0 (0)	1 (1.2)	
Pneumonia	2 (0.7)	2 (2.6)	
Pleural effusion	2 (0.7)	1 (1.2)	
Other	2 (0.7)	0 (0)	
Postoperative stay, days	6 (5–7)	6 (5–8)	0.367
R1 resection	32 (11.5)	10 (13)	0.715
Tumor size, cm	2.0 (1.5–3.0)	2.2 (1.7–2.7)	0.596
Differentiation			0.268
Well or moderate	260 (94)	74 (97)	
Poor	18 (6)	2 (2.6)	
Microvascular invasion	51 (18)	14 (18)	1.000
Capsular invasion	112 (40)	30 (39)	0.964
Recurrence	136 (49)	42 (55)	0.353

Data are presented as *n*, *n*(%), or median (interquartile range)

ARDS acute respiratory distress syndrome

*Statistically significant

Table 7 shows the postoperative recurrence patterns, details of additional treatment after recurrence, and causes of death. While recurrence was mostly intrahepatic in all three groups (Child–Pugh A vs. B7 vs. B8/9: 90% vs. 95% vs. 95%, respectively; $P = 0.150$), the incidence of local recurrence was low (8% vs. 5% vs. 4.5%, respectively; $P = 0.310$). There was no significant difference in the proportion of retreatment after recurrence among the three groups (Child–Pugh A vs. B7 vs. B8/9: 77% vs. 70% vs. 59%, respectively; $P = 0.172$). While all patients in the

Fig. 1 **A** Recurrence-free survival in the early and advanced cirrhotic groups. **B** Overall survival in the early and advanced cirrhotic groups
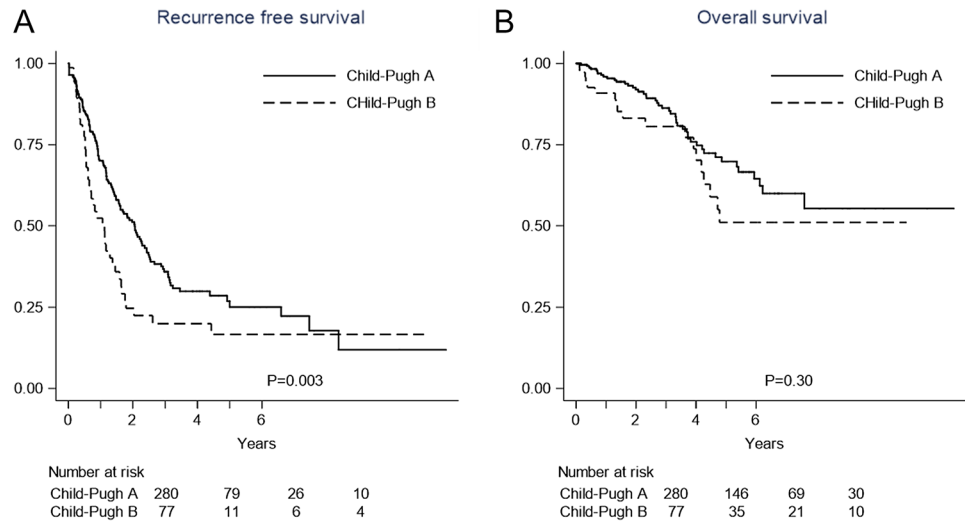
Discussion

HCC is a heterogeneous disease in terms of its biological and clinical behavior [2, 6]. Even in the current era of multidisciplinary patient care, surgery is still considered the only potentially curative treatment option for HCC [47, 48]. In this reappraisal of current surgical practice for patients with HCC in the setting of Child–Pugh B cirrhosis, we investigated whether careful selection of candidates and minimization of surgical stress by LLR can decrease the rate of adverse events, offering good long-term outcomes including high RFS and OS rates with adjustment for clinical and pathological characteristics. The patients in our study are comparable with those in previous studies in terms of the demographic distribution and tumor-related details [18, 23]. Therefore, we consider that analysis of risk factors for recurrence and survival stratified by the Child–Pugh grade is feasible.

The present study revealed several important findings that may be useful for operative decision-making. Previous studies have suggested that LLR may provide acceptable outcomes in carefully selected patients with cirrhosis [24, 25]. However, these studies compared the combined outcomes of patients with early and advanced cirrhosis versus patients without cirrhosis, making it difficult to apply the results specifically to patients with Child–Pugh B cirrhosis. The present study showed that patients with Child–Pugh B cirrhosis were more likely to develop complications and that they had significantly poorer RFS compared with patients with Child–Pugh A cirrhosis; however, Child–Pugh

B cirrhosis was not significantly associated with OS in the univariate and multivariate analyses. To analyze Child–Pugh B cirrhosis in more detail, the patients with Child–Pugh B cirrhosis were categorized by their Child–Pugh score into the following two groups: those with a Child–Pugh score of 7 (Child–Pugh B7 cirrhosis) and those with a score of 8 or 9 (Child–Pugh B8/9 cirrhosis). Patients in the Child–Pugh B8/9 group were significantly more likely to develop complications than were patients in the other two groups. The univariate analysis and Kaplan–Meier plots showed poorer RFS and OS in the Child–Pugh B8/9 group than in the Child–Pugh A group, but there was no significant difference between the Child–Pugh A and B7 groups. In the multivariate analysis, patients with Child–Pugh B8/9 cirrhosis were more likely to develop recurrence than were patients with Child–Pugh A cirrhosis, but there was no significant association between Child–Pugh A and B7 cirrhosis. Neither Child–Pugh B7 nor B8/9 cirrhosis was an independent risk factor for OS. Our results imply that patients who have HCC with Child–Pugh B7 cirrhosis may be good candidates for LLR, like patients with Child–Pugh A cirrhosis, based on the lack of significant differences in complication rates and RFS. For patients with Child–Pugh B8/9 cirrhosis, LLR should be more carefully considered because these patients have significantly more complications and poorer RFS.

The Child–Pugh B grade encompasses widely varying degrees of liver function impairment, and the clinical condition differs among individual patients. Therefore, the most beneficial and recommended treatment modality in this setting remains controversial [15, 17]. With the recent interest in broadening patients' eligibility for liver resection, most surgeons believe that well-selected patients with Child–Pugh B cirrhosis should not be excluded from the outset because of the potential for good short- and long-term outcomes [34, 49]. LLR, which is considered a minimally

Child–Pugh B7 and B8/9 groups died of HCC recurrence or liver failure, 14 (32%) of the 44 patients in the Child–Pugh A group died of non-liver-related diseases.

Table 3 Univariate and multivariate analyses for RFS and OS in Child–Pugh A and B cirrhosis

Variables	Recurrence-free survival						Overall survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age, years												
≤70	Reference			Reference			Reference					
>70	1.57	1.15–2.14	0.005*	1.44	1.03–2.02	0.032*	1.17	0.69–1.98	0.552			
Sex												
Male	Reference			Reference			Reference					
Female	0.87	0.62–1.24	0.421	0.83	0.57–1.21	0.338	0.72	0.40–1.32	0.288			
BMI (≥24 kg/m²)												
≤24 kg/m²	Reference			Reference			Reference			Reference		
>24 k/m²	1.04	0.76–1.41	0.827	0.98	0.70–1.38	0.917	0.76	0.44–1.30	0.314	0.61	0.34–1.07	0.084
Viral infection												
No	Reference			Reference			Reference					
Yes	0.78	0.56–1.10	0.121	0.74	0.51–1.08	0.121	0.79	0.45–1.40	0.421			
Tumor size (>2 cm)												
≤2 cm	Reference			Reference			Reference			Reference		
>2 cm	1.39	1.02–1.89	0.034*	1.25	0.90–1.75	0.185	2.12	1.24–3.61	0.006*	2.17	1.22–3.87	0.008*
Tumor number												
Single nodule	Reference			Reference			Reference					
Multiple nodules (≥2)	2.00	1.21–3.33	0.007*	2.33	1.42–3.82	0.001*	1.76	0.84–3.72	0.136			
Differentiation												
Well/moderate	Reference			Reference			Reference			Reference		
Poor/others	2.3	1.29–4.21	0.005*	1.69	0.89–3.21	0.112	5.07	2.25–11.4	<0.001*	4.09	1.76–9.53	0.001*
Microvascular invasion												
No	Reference			Reference			Reference			Reference		
Yes	1.50	1.04–2.19	0.032*	1.34	0.89–2.02	0.155	1.71	0.94–3.13	0.080	1.087	0.56–2.10	0.802
Capsule involvement												
No	Reference			Reference			Reference					
Yes	1.21	0.88–1.67	0.243	1.18	0.84–1.65	0.347	1.19	0.70–2.04	0.518			
Pre-locoregional therapy												
No	Reference			Reference			Reference					
Yes	1.62	1.17–2.26	0.004*	1.84	1.28–2.63	0.001*	1.22	0.68–2.20	0.511			
Pre-resection												
No	Reference			Reference			Reference					
Yes	1.59	1.07–2.37	0.022*	1.53	0.99–2.35	0.054	0.75	0.32–1.73	0.490			

Table 3 (continued)

Variables	Recurrence-free survival						Overall survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Portal hypertension												
No	Reference			Reference			Reference					
Yes	1.09	0.80–1.49	0.593	0.84	0.55–1.27	0.402	1.42	0.85–2.36	0.182			
Transfusion												
No	Reference			Reference			Reference			Reference		
Yes	1.46	0.99–2.15	0.056	1.48	0.92–2.37	0.102	1.69	0.95–3.01	0.075	1.92	1.00–3.70	0.050*
Margin status												
R0 resection	Reference			Reference			Reference			Reference		
R1 resection	1.64	1.10–2.45	0.016*	1.61	1.03–2.51	0.035*	1.58	0.85–2.93	0.144	1.91	0.99–3.67	0.053
Child–Pugh grade												
A	Reference			Reference			Reference			Reference		
B	1.70	1.19–2.42	0.003*	2.09	1.33–3.29	0.001*	1.36	0.76–2.45	0.302	1.17	0.61–2.24	0.646

HR hazard ratio, *CI* confidence interval, *BMI*, body mass index

*Statistically significant

Table 4 Characteristics of patients in Child–Pugh A, B7, and B8/9 cirrhosis

Characteristic	Child–Pugh grade			
	Child–Pugh A ($n=280$)	Child–Pugh B7 ($n=42$)	Child–Pugh B8/9 ($n=35$)	*P* value
Age, years	71 (65–77)	71 (67–75)	70 (65–74)	0.531
Sex, male	209 (75)	31 (74)	22 (63)	0.302
BMI, kg/m^2	23.4 ± 3.5	23.9 ± 3.9	26.0 ± 4.6	<0.001*
ASA score				0.599
≤2	235 (84)	35 (83)	27 (77)	
>2	45 (16)	7 (17)	8 (23)	
Hypertension	130 (46)	16 (38)	12 (34)	0.274
Diabetes	93 (33)	12 (29)	12 (34)	0.820
Viral infection, positive	187 (67)	26 (62)	21 (60)	0.633
Cancer stage				0.749
IA–IB	214 (76)	33 (79)	25 (71)	
II–IIIB	66 (24)	9 (21)	10 (29)	
MELD score	7 (6–10)	9 (8–11)	11 (9–12)	0.012*
ALBI score				<0.001*
Grade 1	168 (60)	2 (4.8)	0 (0)	
Grade 2	112 (40)	40 (95.2)	27 (77.1)	
Grade 3	0 (0)	0 (0)	8 (22.9)	
JIS score				<0.001*
0–1	229 (82)	14 (33)	14 (40)	
2–5	51 (18)	28 (67)	21 (60)	
Previous treatment				
Locoregional therapy	77 (28)	6 (14)	7 (20)	0.139
Resection	46 (16)	3 (7.1)	4 (11)	0.274
Platelet count, × 10^3/μL	142 ± 61	88.8 ± 46	89.6 ± 33	<0.001*
Albumin, g/dL	3.9 (3.7–4.2)	3.35 (3.2–3.5)	3.1 (2.7–3.3)	<0.001*
Bilirubin, mg/dL	0.6 (0.5–0.8)	1.1 (0.7–1.4)	1.1 (0.8–1.8)	<0.001*
PT, %	89 (80–97)	67 (64–74)	61 (55–67)	<0.001*
AFP, ng/mL	7.2 (3.6–28.1)	11.1 (3.6–71.2)	9.1 (4.2–26.9)	0.511
PIVKA-II, mAU/mL	33 (22–103)	39 (21–113)	40 (21–179)	0.970
Preoperative ascites	37 (13)	20 (48)	29 (83)	0.001*
Preoperative encephalopathy	2 (0.7)	2 (4.8)	7 (20)	<0.001*
Portal hypertension	75 (27)	32 (76)	20 (71)	<0.001*
ICG retention rate, %	14 (8.1–20.1)	33 (25.8–39.5)	45 (29.8–52.0)	<0.001*

Data are presented as median (interquartile range), *n* (%), or mean ± standard deviation

BMI body mass index, *ASA* American Society of Anesthesiologists, *ALBI* albumin-bilirubin, *MELD* Model for End-stage Liver Disease, *JIS* Japan Integrated Staging, *PT* prothrombin time, *AFP* alpha-fetoprotein, *ICG* indocyanine green

*Statistically significant

invasive approach, may be effective in such patients with advanced cirrhosis [24]. Compared with open surgery, LLR is expected to reduce the rates of complications, liver decompensation, and ascites production because of preservation of collaterals, reduced liver mobilization, and less severe electrocyte imbalance [19, 50, 51]. A recent study comparing LLR and open liver resection for the treatment of HCC in patients with Child–Pugh B cirrhosis revealed that large blood loss, overall morbidity, and postoperative liver decompensation leading to a long hospital stay were less likely to occur in LLR than in open liver resection [23]. However, because there are very few cases of LLR for HCC in patients with advanced cirrhosis in previous studies, LLR is not currently established as technically or oncologically safe for the treatment of HCC in patients with advanced cirrhosis compared with early cirrhosis [26]. In the present study, using the IWATE difficulty scoring systems validated in a previous paper, which were shown to correlate with postoperative complications [32], we evaluated the complexity of LLR and found no significant differences in the

Table 5 Perioperative outcomes of patients in Child–Pugh A, B7, and B8/9 cirrhosis

Characteristic	Child–Pugh grade			
	Child–Pugh A ($n=280$)	Child–Pugh B7 ($n=42$)	Child–Pugh B8/9 ($n=35$)	P value
Position of lesion				0.771
Left	105	19	14	
Right anterior	77	8	11	
Right posterior	65	12	8	
Caudate	8	1	0	
Multiple	25	3	2	
Type of hepatectomy				0.003*
Non-anatomical	240 (86)	41 (98)	35 (100)	
Anatomical	40 (14)	1 (2)	0 (0)	
Difficulty score				0.490
Low (1–3)	143 (51)	17 (40)	15 (43)	
Intermediate (4–6)	128 (45)	22 (52)	19 (54)	
Advanced (7–9)	8 (2.9)	3 (7.1)	1 (2.9)	
Expert (10–12)	1 (0.4)	0	0	
Operative time, minutes	167 (121–223)	169 (123–217)	140 (118–204)	0.427
Blood loss, mL	30 (0–100)	35 (0–100)	30 (0–150)	0.921
Transfusion	26 (9.3)	18 (43)	14 (40)	<0.001*
90-day mortality	1 (0.4)	0 (0)	2 (5.7)	0.032
Major morbidity (Clavien–Dindo grade > II)	11 (3.9)	2 (4.8)	4 (11)	0.117
Complications	23 (8.2)	4 (9.6)	9 (26)	0.010*
Ascites	7 (2.5)	2 (4.8)	5 (14)	
Liver failure	0 (0)	0 (0)	1 (2.9)	
Bile leakage	3 (1.1)	0 (0)	0 (0)	
Delayed biliary stricture	2 (0.7)	0 (0)	0 (0)	
Abdominal collection	3 (1.1)	0 (0)	1 (2.9)	
Bleeding	2 (0.7)	0 (0)	0 (0)	
ARDS	0 (0)	0 (0)	1 (2.9)	
Pneumonia	2 (0.7)	2 (4.8)	0 (0)	
Pleural effusion	2 (0.7)	0 (0)	1 (2.9)	
Other	2 (0.7)	0 (0)	0 (0)	
Postoperative stay, days	6 (5–7)	6 (5–8)	6 (5–8)	0.425
R1 resection	32 (11.5)	4 (9.5)	6 (17)	0.539
Tumor size, cm	2.0 (1.5–3.0)	2.3 (1.8–2.8)	2.1 (1.5–2.7)	0.548
Differentiation				0.371
Well or moderate	260 (94)	39 (95)	35 (100)	
Poor	18 (6)	2 (5)	0 (0)	
Microvascular invasion	51 (18)	4 (9.5)	10 (28)	0.093
Capsular invasion	112 (40)	14 (35)	16 (46)	0.640
Recurrence	136 (49)	20 (48)	22 (63)	0.268

Data are presented as *n*, *n*(%), or median (interquartile range)

ARDS acute respiratory distress syndrome

*Statistically significant

difficulty scores for both the two groups of Child–Pugh A and B (*P* = 0.348) and the three groups of Child–Pugh A, B7, and B8/9 (*P* = 0.490). We therefore consider that the impact of the complexity of LLR on the comparison of complication rates between these groups was limited. Even minimally invasive LLR did not eliminate the difference in postoperative complications between the Child–Pugh A and B groups, and postoperative RFS was significantly worse in

Fig. 2 A Recurrence-free survival stratified by Child–Pugh A, B7, and B8/9 cirrhosis. **B** Overall survival stratified by Child–Pugh A, B7, and B8/9 cirrhosis
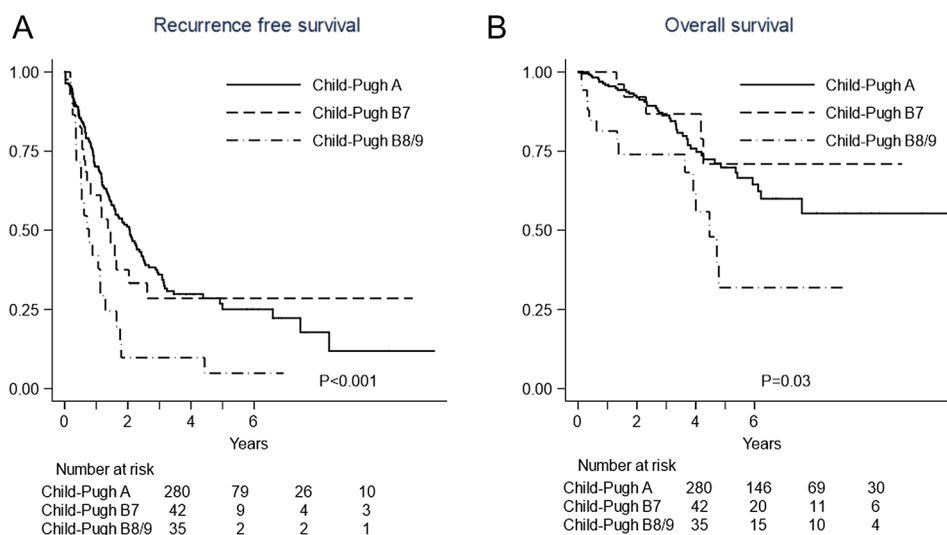
the Child–Pugh B group. However, the complication rate in the Child–Pugh B group was 17% ($n = 13$), 7.8% ($n = 6$) of major morbidities were Clavien–Dindo grade $\geq$ III, and no in-hospital mortality occurred. The 90-day mortality rate was 2.6% ($n = 2$); one patient developed liver failure due to gastrointestinal bleeding associated with esophageal varices, and the other developed liver failure due to cirrhosis with refractory ascites, probably caused by surgical invasion. Although the proportion of complications in the Child–Pugh B group were significantly higher than that in the Child–Pugh A group, there were no significant differences in major morbidities, the length of hospital stay, or 90-day mortality between the two groups. Moreover, when the Child–Pugh B group was divided into the Child–Pugh B7 and Child–Pugh B8/9 groups, there were no significant differences in postoperative complications (including serious complications), RFS, or OS between the two groups, and Child–Pugh B7 cirrhosis was not an independent prognostic factor for RFS or OS in the multivariate analysis. Death within 90 days occurred in one patient in the Child–Pugh A group who died of cancer recurrence and in two patients in the Child–Pugh B8/9 group; however, there was no 90-day mortality in the Child–Pugh B7 group. We believe that LLR can be performed without loss of technical or oncological safety in patients with Child–Pugh B7 cirrhosis.

Whether LLR is beneficial for patients with Child–Pugh 8/9 cirrhosis remains controversial. However, although the patients in the Child–Pugh B8/9 group had a 3-year RFS rate of only 10%, they had a reasonable 3-year OS rate of approximately 77% following resection, which was better than that in historical cohorts of patients treated with TACE or sorafenib [16, 17]. Considering the possibility of cure by resection and the low incidence of serious postoperative complications, we believe that it makes sense to perform LLR in suitable cases. For example, good candidates for

LLR may include patients with Child–Pugh 8/9 cirrhosis who have tumors protruding at the liver edge that make radiofrequency ablation difficult and patients with hypovascular HCC for which TACE is not feasible [52]. In addition, multidisciplinary treatment has been shown to be important to improve the prognosis of HCC [53, 54]. In the present study, although patients in the Child–Pugh B group were less likely to undergo liver resection as a treatment for recurrence than those in the Child–Pugh A group, about 60% of patients in the Child–Pugh 8/9 group who developed recurrence after surgery were able to receive any type of retreatment and the proportion of patients with recurrence who received retreatment was not significantly different from that in the Child–Pugh A group. Minimally invasive LLR may decrease the postoperative decline in the patient's general condition and may be less likely to interfere with retreatment. We consider that the designation of Child–Pugh 8/9 cirrhosis should not be an a priori contraindication to surgery, especially when patients present with resectable tumors.

There are several possible reasons why Child–Pugh B8/9 cirrhosis was not significantly associated with OS. One explanation is that because of the small sample size of the Child–Pugh B8/9 group, the deaths caused by non-liver-related diseases in the Child–Pugh A group may have influenced the results of this study. In fact, whereas all deaths in the Child–Pugh B8/9 group were due to either recurrence of HCC or liver failure, one-third of deaths in the Child–Pugh A group were caused by conditions other than liver-related disease. Another explanation is that multidisciplinary patient care can make it easier to control HCC even in patients with poor liver function. We found that patients in the Child–Pugh B8/9 group, as in the other groups, were able to receive post-recurrence retreatment including surgery, radiofrequency ablation, TACE, chemotherapy, CyberKnife radiosurgery, or a combination of these treatments [53, 54].

Table 6 Univariate and multivariate analyses for RFS and OS in Child–Pugh A, B7, and B8/9 cirrhosis

Variable	Recurrence-free survival						Overall survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age, years												
≤70	Reference			Reference			Reference					
>70	1.57	1.15–2.14	0.005*	1.47	1.06–2.05	0.022*	1.17	0.69–1.98	0.552			
Sex												
Male	Reference			Reference			Reference					
Female	0.87	0.62–1.24	0.421	0.83	0.56–1.21	0.327	0.72	0.40–1.32	0.288			
BMI (≥24 kg/m^2)												
≤24 kg/m^2	Reference			Reference			Reference			Reference		
>24 kg/m^2	1.04	0.76–1.41	0.827	1.01	0.71–1.42	0.974	0.76	0.44–1.30	0.314	0.64	0.36–1.12	0.120
Viral infection												
No	Reference			Reference			Reference					
Yes	0.78	0.56–1.10	0.153	0.75	0.52–1.09	0.135	0.79	0.45–1.40	0.421			
Tumor size (>2 cm)												
≤2 cm	Reference			Reference			Reference			Reference		
>2 cm	1.39	1.02–1.89	0.034*	1.27	0.91–1.77	0.167	2.12	1.24–3.61	0.006*	2.12	1.29–3.78	0.011*
Tumor number												
Single nodule	Reference			Reference			Reference					
Multiple nodules (≥2)	2.00	1.21–3.33	0.007*	2.39	1.45–3.93	0.001*	1.76	0.84–3.72	0.136			
Differentiation												
Well/moderate	Reference			Reference			Reference			Reference		
Poor/others	2.3	1.29–4.21	0.005*	1.75	0.92–3.33	0.090	5.07	2.25–11.4	<0.001*	4.46	1.89–10.5	0.001*
Microvascular invasion												
No	Reference			Reference			Reference			Reference		
Yes	1.50	1.04–2.19	0.032*	1.28	0.85–1.93	0.240	1.71	0.94–3.13	0.080	0.982	0.50–1.93	0.959
Capsule involvement												
No	Reference			Reference			Reference					
Yes	1.21	0.88–1.67	0.243	1.15	0.82–1.62	0.409	1.19	0.70–2.04	0.518			
Pre-locoregional therapy												
No	Reference			Reference			Reference					
Yes	1.62	1.17–2.26	0.004*	1.90	1.32–2.72	<0.001*	1.22	0.68–2.20	0.511			
Pre-resection												
No	Reference			Reference			Reference					
Yes	1.59	1.07–2.37	0.022*	1.55	1.01–2.38	0.047*	0.75	0.32–1.73	0.490			

Table 6 (continued)

| Variable | Recurrence-free survival | | | | | | Overall survival | | | | | |
| | Univariate analysis | | | Multivariate analysis | | | Univariate analysis | | | Multivariate analysis | | |
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Portal hypertension												
No	Reference			Reference			Reference					
Yes	1.09	0.80–1.49	0.593	0.89	0.59–1.34	0.565	1.42	0.85–2.36	0.182			
Transfusion												
No	Reference			Reference			Reference			Reference		
Yes	1.46	0.99–2.15	0.056	1.47	0.91–2.36	0.112	1.69	0.95–3.01	0.075	1.93	1.00–3.71	0.050*
Margin status												
R0 resection	Reference			Reference			Reference			Reference		
R1 resection	1.64	1.10–2.45	0.016*	1.50	0.96–2.35	0.075	1.58	0.85–2.93	0.144	1.81	0.94–3.49	0.077
Child–Pugh grade												
A	Reference			Reference			Reference			Reference		
B7	1.22	0.75–1.97	0.428	1.39	0.77–2.50	0.271	0.67	0.24–1.88	0.450	0.60	0.21–1.73	0.342
B8/9	2.61	1.65–4.13	<0.001*	3.15	1.87–5.31	<0.001*	2.17	1.12–4.20	0.022*	1.80	0.86–3.74	0.118

HR hazard ratio, *CI* confidence interval, *BMI* body mass index

*Statistically significant

Table 7 Postoperative recurrence patterns, details of additional treatment after recurrence, and causes of death

	Patients with recurrence			
	Child–Pugh A (*n*=136)	Child–Pugh B7 (*n*=20)	Child–Pugh B8/9 (*n*=22)	*P* value
Recurrence site				
Local recurrence in the liver	11	1	1	
Intrahepatic	123	19	21	
Bone	1	0	0	
Peritoneal dissemination	1	0	0	
Retreatment after recurrence	105 (77%)	14 (70%)	13 (59%)	0.172
Hepatectomy	20	2	1	
RFA	12	1	1	
TACE	23	3	5	
Chemotherapy	6	1	0	
CyberKnife	6	0	1	
Hepatectomy+RFA	2	0	0	
Hepatectomy+TACE	1	0	0	
Hepatectomy+chemotherapy	4	0	0	
Hepatectomy+CyberKnife	2	0	0	
RFA+TACE	11	2	0	
RFA+chemotherapy	1	0	0	
RFA+CyberKnife	1	0	1	
TACE+chemotherapy	9	4	2	
TACE+CyberKnife	4	0	1	
Chemotherapy+CyberKnife	0	1	0	
More than 3 procedures	3	0	1	
	Patients who died			
	Child–Pugh A (*n*=44)	Child–Pugh B7 (*n*=4)	Child–Pugh B8/9 (*n*=11)	
HCC recurrence	24	3	4	
Liver failure	6	1	7	
Pneumonia	4	0	0	
Cerebrovascular disease	2	0	0	
Leukemia	2	0	0	
Cardiovascular disease	1	0	0	
Other cancer	1	0	0	
Unknown	4	0	0	

RFA radiofrequency ablation, *TACE* transarterial chemoembolization, *HCC* hepatocellular carcinoma

Our study had several limitations. First, the pooled analysis using a database from a single institution may have introduced some selection bias. We believe that the indications for surgery, especially in patients with Child–Pugh B cirrhosis, were comparable with those in previous studies; however, they were not necessarily generalized. Second, patients with Child–Pugh B cirrhosis often have no option but limited non-anatomical resection, and such patients constituted the majority in our study. Despite the ongoing debate regarding anatomical versus non-anatomical resection for HCC and the related influence on survival [55], we believe that the type of hepatectomy should be balanced with the actual clinical condition in patients with Child–Pugh B cirrhosis to increase the chance of a better prognosis. Third, Child–Pugh status was an independent risk factor for RFS, but its HR was not very high compared with other factors. The postoperative improvement in liver function due to medical therapies, such as elimination of hepatitis C virus and improvement in nutritional status and ascites, may have influenced the differences in outcomes between the Child–Pugh A and B groups. Fourth, because of the relatively small sample size of the current study, it is possible that the covariates were not fully adjusted, especially OS. Although not statistically significant, OS was better in the Child–Pugh B7 group than

in the Child–Pugh A group; however, the small number of deaths in the Child–Pugh B7 group makes an accurate evaluation difficult. Fifth, differences in the type of treatment, such as the use of lenvatinib and CyberKnife radiosurgery, between the early and late periods of this study may have affected OS [56, 57]. However, the strategy for recurrent HCC at our institution is the optimal treatment according to the guidelines of the Japan Society of Hepatology of the era of the study period, and we believe that the emergence of novel therapies had only a limited influence on the present study. Finally, because liver transplantation was not considered in this study, further improvement in the prognosis may be expected if liver transplantation becomes a more common treatment for Child–Pugh B cirrhosis [49].

In conclusion, we examined the prognostic value of Child–Pugh B cirrhosis in patients undergoing LLR for HCC. Even LLR, which is considered minimally invasive surgery, was associated with more complications and poorer RFS in patients with Child–Pugh B cirrhosis than Child–Pugh A cirrhosis. However, when Child–Pugh B8/9 and Child–Pugh B7 cirrhosis were examined separately, the overall complication rates, RFS, and OS were comparable between patients with Child–Pugh B7 and Child–Pugh A cirrhosis. In contrast, the overall complication rates and RFS were significantly worse in patients with Child–Pugh B8/9 than Child–Pugh A cirrhosis. Based on these results, patients with Child–Pugh B7 cirrhosis are appropriate candidates for LLR, with the aim of safely optimizing the chance for cure and the long-term oncological outcomes. More careful decision-making regarding LLR and perioperative management is necessary for patients with Child–Pugh B8/9 cirrhosis.

Declarations

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