Original Article

DOI: 10.5582/bst.2024.01277

Laparoscopic versus open liver resection for intrahepatic cholangiocarcinoma: Stratified analysis based on tumor burden score

Hongxin Li[1,§], Junjie Kong[2,§], Wei Si[2], Tao Wang[3], Min Ji[4], Guangbing Li[2,*], Jun Liu[1,2,*]

[1] Department of Liver Transplantation and Hepatobiliary Surgery, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Ji'nan, Shandong, China;
[2] Department of Liver Transplantation and Hepatobiliary Surgery, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Ji'nan, Shandong, China;
[3] Department of Liver Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan, China;
[4] Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital of Zhengzhou University.

SUMMARY The role of laparoscopic liver resection (LLR) for intrahepatic cholangiocarcinoma (ICC) remains debated. This study aimed to evaluate the short- and long-term outcomes of LLR vs. open liver resection (OLR) in ICC stratified by tumor burden score (TBS). ICC patients who underwent LLR or OLR were included from a multicenter database between July 2009 and October 2022. Patients were stratified into two cohorts based on whether the TBS was > 5.3. A 1:3 propensity score matching (PSM) analysis was performed between LLR and OLR in each cohort. Cox regression analysis was used to identify prognostic factors for ICC. A total of 626 patients were included in this study, 304 and 322 patients were classified into the low- and high-TBS groups, respectively. In the low-TBS group, after PSM, LLR was associated with less blood loss, lower CCI, fewer complications and shorter hospital stay (all $p < 0.05$). Kaplan-Meier curves revealed that LLR had better OS ($p = 0.032$). Multivariate Cox regression analysis showed that surgical procedure was an independent prognostic factor for ICC (HR: 0.445; 95% CI: 0.235-0.843; $p = 0.013$). In the high-TBS group, after PSM, LLR were associated with reduced blood loss, lower CCI, fewer complications and shorter hospital stay (all $p < 0.05$), while OS ($p = 0.98$) and DFS ($p = 0.24$) were similar between the two groups. TBS is an important prognostic factor for ICC. LLR is a safe and feasible option for ICC and leads to faster postoperative recovery. LLR can offer ICC a comparable and even better long-term prognosis than OLR.

Keywords tumor burden score, intrahepatic cholangiocarcinoma, laparoscopic liver resection, open liver resection, propensity score matching

1. Introduction

Intrahepatic cholangiocarcinoma (ICC), which arises from the epithelial cells of the intrahepatic bile duct, is the second most common primary liver cancer, accounting for up to 20% of all liver malignancies and 3% of gastrointestinal malignancies (*1,2*). The incidence of ICC has consistently increased over the past four decades (*3*). In the USA, this rate is increasing, with an annual percentage change of 2.3%, from 0.44 to 1.18 cases per 100,000 people between 1973 and 2012 (*3*). Surgical resection remains the first-line treatment strategy for ICC, which could be the only potential cure and provide a 5-year overall survival (OS) ranging from 20% to 35% (*4*).

Recently, with the development of laparoscopic instruments and progress in surgical experience, laparoscopic liver resection (LLR) has been widely performed for the treatment of liver disease (*5,6*). Compared with open liver resection (OLR), LLR is associated with decreased tissue damage, less blood loss, lower occurrence of complications and a shorter hospital stay (*7,8*). Although ICC is not a contraindication for LLR, due to concerns of inadequate resection margins, uncontrollable hemorrhage and failure of lymph node dissection (LND), few reports on this topic are available (*9*). Moreover, previous studies have focused mainly on the resection of small solitary ICCs, and data related to the application of LLR for large or multiple ICCs are scarce (*10*). The feasibility and safety of LLR for varying sizes or numbers of ICCs has yet to be fully elucidated. Consequently, selecting the optimal surgical strategy for

ICC remains a troublesome problem.

Tumor Burden Score (TBS), introduced in 2017, serves as a prognostic tool derived from tumor size and number and is primarily intended for colorectal liver metastases (CRLM) (*11*). Recently, TBS has been applied to stratify the prognosis of several different cancers in the liver, including hepatocellular carcinoma, ICC and CRLM (*11-14*). As such, the objective of this study was to compare the clinical characteristics of different TBS groups among patients who underwent curative liver resection for ICC using a large, multicenter cohort of patients. In addition, we sought to compare the short- and long-term outcomes between LLR and OLR for ICC treatment in different TBS groups in a case-matched analysis *via* propensity score matching (PSM) and to identify perioperative variables that influence ICC prognosis, which could provide clinicians with insights into surgical options and improve the prognosis of ICC patients.

2. Materials and Methods

2.1. Patient selection

Patients who underwent curative-intent liver resection between June 2009 and October 2022 at Shandong Provincial Hospital Affiliated to Shandong First Medical University, West China Hospital of Sichuan University and The First Affiliated Hospital of Zhengzhou University were enrolled. This study was approved by the Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University, West China Hospital of Sichuan University and The First Affiliated Hospital of Zhengzhou University, and informed consent was obtained from all patients.

Patients who met the following criteria were selected: *i*) ICC diagnosed based on postoperative histopathology; *ii*) good liver function, Child–Pugh class A/B (score ≤ 7); and *iii*) curative hepatectomy. The exclusion criteria were as follows: *i*) palliative hepatectomy (R1 or R2); *ii*) patients who were converted to laparotomy after endoscopic surgery; *iii*) patients with extrahepatic metastasis or recurrent liver cancer; *iv*) patients who had received neoadjuvant therapy; and *v*) patients with incomplete follow-up data.

2.2. TBS definition and TBS grade evaluation

Preoperative imaging reports were collected for each enrolled patient to obtain accurate maximum tumor diameter and tumor number data. TBS is defined as the distance of two variables, the maximum tumor diameter (x-axis) and the tumor number (y-axis), from the origin of the Cartesian plane. The formula applies Pythagoras 'theorem: TBS^2 = (maximum tumor diameter)^2 + (number of tumors)^2. X-tile software was used to determine the optimal cut-off value for TBS (5.30 units) (*15*). Patients were subsequently divided into high- and low-TBS groups according to the optimal cut-off value.

2.3. Data collection and liver resection

All patient information, including demographic details, preoperative laboratory data, surgery-related parameters and postoperative outcomes, was reviewed and retrieved from hospital electronic medical records. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated as follows: NLR = absolute neutrophil count/absolute lymphocyte count; PLR = absolute platelet count/absolute lymphocyte count (*16,17*). Surgical complications were evaluated according to the Clavien–Dindo (CDc) classification system and comprehensive complication index (CCI) (*18,19*). Tumor staging was determined according to the American Joint Committee on Cancer (AJCC) 8th Edition staging system. All procedures were performed by experienced hepatobiliary surgeons. Before performing surgery, patients and their families must understand the pros and cons of LLR and OLR; we discuss the risks of surgery with them, and finally make decisions based on the patient's own situation.

2.4. Follow-up

Patients need regular follow-up after surgery, first in the first month after discharge to the outpatient clinic for the first re-examination; every three months for the next two years; and from the third year to the hospital every six months for re-examination, until death or loss to follow-up. The examinations included liver function tests, serum alpha-fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9), carbohydrate antigen 125 (CA125), carcinoembryonic antigen (CEA), and enhanced abdominal CT or magnetic resonance imaging (MRI) examinations. Recurrence was defined as local recurrence or distant metastasis detected by dynamic contrast-enhanced CT or MRI. OS was calculated from the time of liver resection to the last follow-up or death from any cause. Disease-free survival (DFS) was calculated from the time of hepatectomy to the last follow-up or tumor recurrence. The follow-up data were collected as of 31 August 2023.

2.5. Statistical analysis

Continuous variables are expressed as medians and interquartile ranges (IQRs) and were compared using the Mann–Whitney *U* test. Categorical variables are expressed as numbers (percentages) and were analyzed *via* the chi-square test or Fisher's exact test. Survival curves were generated using the Kaplan–Meier method and compared *via* the log-rank test. The patients were categorized into a high TBS group (n = 322) and a low TBS group (n = 304) based on an optimal TBS cut-

off value of 5.30. To mitigate discrepancies in baseline characteristics between the LLR and OLR groups, a 1:3 propensity score matching was conducted utilizing nearest neighbor matching within both the high and low TBS groups. The covariates employed for achieving balance included all baseline variables, excluding surgical outcomes, with a caliper radius established at a standard deviation of 0.02 to ensure adequate matching quality. After the matching, continuous variables were compared using the Mann-Whitney *U* test, while categorical variables were assessed through the chi-square test or Fisher's exact test to identify any residual imbalances. Univariate and multivariate Cox proportional hazards models were used to identify prognostic factors associated with OS. In univariate analyses, variables with $p < 0.1$ were considered worthy of inclusion in multivariate analyses. The optimal cut-off value of TBS was calculated *via* X-tile software (3.6.1). All other statistical analyses were performed using SPSS software (27.0) and R (4.4.0). All tests were two-tailed, and a p value < 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the entire study population

The flow chart of this study is shown in Figure 1. A total of 947 liver resections for ICC were conducted during the study period, of which 626 patients who underwent curative liver resection and met the inclusion criteria were enrolled. The baseline characteristics of the 626 patients are shown in Table 1. The median age was 59.0 years, with 339 male patients (54.2%). A total of 243 (38.8%) patients received LND, while 127 (20.3%) patients underwent LLR. The median diameter of the largest lesion was 5.3 cm, while multiple tumors were present in 89 (14.2%) of the patients; consequently, the median TBS was 5.49.

The optimal cut-off value of the TBS for OS was determined to be 5.30 according to X-tile analysis (Supplemental Figure S1, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=230*). Accordingly, 304 patients (48.6%) and 322 patients (51.4%) were classified into the low- and high-TBS groups, respectively. Patients with high TBS disease more often had poorer oncologic features and worse preoperative laboratory tests. The KM analysis revealed that patients in the high-TBS group had a significantly poorer prognosis than those in the low-TBS group ($p <$ 0.01).

3.2. Patient characteristics between different surgical procedures in the low- and high-TBS groups

Table 2 presents the baseline characteristics of the participants in the low-TBS cohort. A total of 68 (22.4%) patients underwent LLR. Before PSM, there were notable differences between the LLR and OLR groups in body mass index (BMI, 23.31 *vs*. 24.34 kg/m^2; $p = 0.020$), platelet (PLT, 176.00 *vs.* 198.00*10^9/L; $p = 0.044$), PLR (107.50 *vs.* 124.81; $p = 0.046$), white blood cell (WBC, 5.90 *vs.* 5.46*10^9/L; $p = 0.019$), neutrophil (NE, 3.69 *vs.* 3.23*10^9/L; $p = 0.019$), aspartate aminotransferase (AST, 27.00 *vs.* 25.00u/L; $p = 0.042$), and CA199 (50.77 *vs.* 28.03 u/mL; $p = 0.003$). Notably, disparities in nerve invasion ($p = 0.048$), lymphatic metastasis ($p = 0.009$), Adjuvant therapy ($p = 0.020$) and TNM stage ($p < 0.001$) were noted between the two groups. After PSM, the OLR group consisted of 93 patients, while the LLR group included 47 patients, with a more balanced distribution of characteristics between the two groups.

The baseline characteristics of patients in the high-TBS cohort are presented in Table 3. The LLR group consisted of 59 (18.3%) ICC patients. Before PSM, there were notable differences between the LLR and OLR groups in BMI (22.84 *vs*. 24.91 kg/m^2; $p < 0.001$), PLT (190.00 *vs*. 233.00*10^9/L; $p < 0.001$), total bilirubin (TB, 13.60 *vs.* 11.50 μmol/L; $p = 0.004$), alanine aminotransferase (ALT, 25.00 *vs.* 19.00 U/L; $p = 0.005$), AST (31.00 *vs*.25.00 U/L; $p < 0.001$), alkaline phosphatase (ALP, 128.00 *vs*. 99.00 U/L; $p < 0.001$), GGT (88.00 *vs.* 51.00 U/L; $p < 0.001$), AFP (3.50 *vs*. 2.70 ng/mL; $p = 0.018$), lymphatic metastasis (24.7 *vs.*

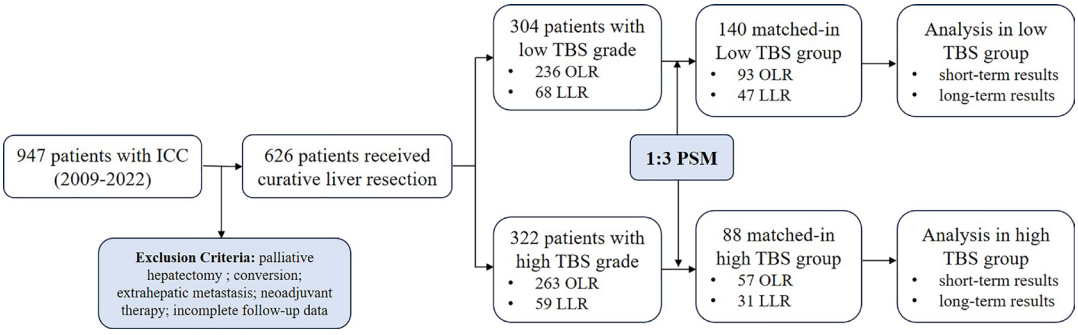

Figure 1. Flow chart of this study showing the selection process of ICC patients who underwent LLR or OLR. ICC intrahepatic cholangiocarcinoma, LLR laparoscopic liver resection, OLR open liver resection, PSM propensity score matching. Because some cases could not simultaneously find effective matching objects, the matching result was not an absolute 1:3.

Table 1. The baseline characteristics and surgical outcomes of ICC patients in the total cohort, low TBS cohort, and high TBS cohort

Variables	The total cohort (*n* = 626)	Low TBS cohort (*n* = 304)	High TBS cohort (*n* = 322)	*p* value
Age, median (IQR), years	59.00 (51.00-65.00)	58.00 (50.00-65.00)	59.00 (51.00-65.00)	0.464
Gender				0.483
Female, *n* (%)	287 (45.8)	135 (44.4)	152 (47.2)	
Male, *n* (%)	339 (54.2)	169 (55.6)	170 (52.8)	
Short stature, median (IQR), m	1.63 (1.57-1.69)	1.63 (1.58-1.70)	1.63 (1.57-1.69)	0.192
Weight, median (IQR), Kg	61.00 (54.14-70.00)	62.28 (54.11-71.00)	60.14 (54.38-68.03)	0.138
BMI, median (IQR), kg/m^2	23.31 (20.96-25.75)	23.67 (20.85-25.93)	23.06 (21.15-25.68)	0.466
Hypertension, *n* (%)	151(24.1)	79 (26.0)	72 (22.4)	0.289
Diabetes, *n* (%)	60 (9.6)	27 (8.9)	33 (10.2)	0.561
Alcohol, *n* (%)	139 (22.2)	62 (20.4)	77 (23.9)	0.290
HBV, *n* (%)	177 (28.3)	90 (29.6)	87 (27.0)	0.473
HCV, *n* (%)	4 (0.6)	4 (1.3)	-	**0.039**
WBC, median (IQR), 10^9/L	6.40 (5.17-7.73)	5.83 (4.78-7.06)	6.96 (5.65-8.18)	**< 0.001**
NE, median (IQR), 10^9/L	4.07 (3.13-5.34)	3.57 (2.81-4.58)	4.55 (3.64-5.77)	**< 0.001**
Lym, median (IQR), 10^9/L	1.53 (1.20-1.89)	1.55 (1.20-1.97)	1.53 (1.21-1.85)	0.426
NLR, median (IQR), %	2.64 (1.86-3.69)	2.2 9(1.62-3.18)	2.98 (2.20-4.28)	**< 0.001**
PLT, median (IQR), 10^9/L	190.00 (138.00-239.50)	182.00 (131.00-230.00)	196.00 (148.75-250.00)	**0.004**
PLR, median (IQR), %	121.28 (88.41-167.12)	110.50 (85.71-151.72)	131.06 (93.57-180.96)	**0.001**
PT, median (IQR), s	1.02 (0.97-1.08)	1.02 (0.97-1.07)	1.01 (0.96-1.08)	0.640
INR, median (IQR), %	11.90 (11.20-12.70)	11.80 (11.20-12.60)	11.90 (11.20-12.83)	0.346
TB, median (IQR), μmol/L	14.40 (10.90-19.20)	15.10 (11.70-20.33)	13.05 (10.25-18.23)	**<0.001**
ALT, median (IQR), U/L	24.00 (16.00-39.00)	25.00 (16.00-41.00)	24.00 (16.00-38.00)	0.175
AST, median (IQR), U/L	28.00 (22.00-39.00)	27.00 (21.00-36.00)	30.00 (24.00-40.25)	**0.012**
ALP, median (IQR), U/L	108.00 (84.50-165.00)	96.00 (77.00-140.00)	121.50 (94.75-181.25)	**< 0.001**
GGT, median (IQR), U/L	65.00 (34.00-154.00)	54.00 (26.00-134.00)	74.00 (43.00-165.50)	**< 0.001**
AFP, median (IQR), ng/mL	3.03 (1.98-5.34)	2.83 (1.90-4.50)	3.36 (2.07-6.09)	**0.002**
CA199, median (IQR), U/mL	58.50 (17.02-558.70)	47.11 (15.70-262.70)	93.15 (20.51-834.03)	**0.001**
CA125, median (IQR), U/ml	18.80 (9.51-61.87)	15.28 (8.65-39.71)	26.55 (10.79-87.44)	**< 0.001**
CEA, median (IQR), ng/mL	2.86 (1.60-5.91)	2.78 (1.54-4.80)	3.02 (1.60-8.06)	0.160
Child–Pugh, *n* (%)				0.917
A	580 (92.7)	282 (92.8)	298 (92.5)	
B	46 (7.3)	22 (7.2)	24 (7.5)	
Nerve invasion, *n* (%)	103 (16.5)	72 (23.7)	31 (9.6)	**< 0.001**
Differentiation, *n* (%)				0.288
Poor	339 (54.2)	158(52.0)	181 (56.2)	
Moderate / Well	287 (45.8)	146(48.0)	141 (43.8)	
Satellite nodules, *n* (%)	75 (12.0)	22 (7.2)	53 (16.5)	**< 0.001**
Lymphatic metastasis, *n* (%)	123 (19.6)	55 (18.1)	68 (21.1)	0.341
Capsular invasion, *n* (%)	326 (52.1)	132 (43.4)	194 (60.2)	**< 0.001**
Maximum tumor size (IQR), cm	5.30 (3.70-7.20)	3.55 (3.00-4.50)	7.00 (6.00-9.00)	**< 0.001**
Multiple tumors, *n* (%)	89 (14.2)	28 (9.2)	61 (18.9)	**< 0.001**
TNM, *n* (%)				**0.008**
I/II	322 (51.4)	173 (56.9)	149 (46.3)	
III/IV	304 (48.6)	131 (43.1)	173 (53.7)	
Operation time (IQR), min	240.00 (180.00-305.00)	210.00 (170.00-278.75)	255.00 (180.00-320.00)	**0.008**
Blood loss (IQR), ml	200.00 (20.00-400.00)	100.00 (20.00-200.00)	300.00 (100.00-400.00)	**< 0.001**
CCI (IQR)	8.70 (8.70-22.60)	8.70 (8.70-22.60)	8.70 (8.70-22.60)	0.833
CD, *n* (%)	82 (13.1)	40 (13.2)	42 (13.0)	0.966
Lymph node dissection, *n* (%)	243 (38.8)	105 (34.5)	138 (42.9)	**0.033**
Length of hospital stay (IQR), d	12.00 (10.00-16.00)	12.00 (9.75-16.00)	13.00 (11.00-17.00)	0.141
Waiting time for surgery (IQR), d	4.00 (3.00-6.00)	4.00 (3.00-5.25)	4.00 (3.00-6.00)	0.759
Postoperative discharge time (IQR), d	8.00 (6.00-11.00)	8.00 (6.00-10.00)	9.00 (7.00-11.00)	0.060
Surgical approach, *n* (%)				0.208
LLR	127 (20.3)	68 (22.4)	59 (18.3)	
OLR	499 (79.7)	236 (77.6)	263 (81.7)	
Adjuvant therapy, *n* (%)	200 (31.9)	93 (30.6)	107 (33.2)	0.479

Data are presented as *n* (%) or median (IQR); Bold text hinted that these variables were statistically significant. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; LLR, laparoscopic liver resection; OLR, open liver resection; PSM, propensity score matching; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; WBC, white blood cells; NE, neutrophils; Lym, lymphocytes; NLR, neutrophil-to-lymphocyte ratio; PLT, platelets; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; AFP, alpha-fetoprotein; CA199, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; CCI, charlson comorbidity index, CD, Clavien–Dindo ≥ III; IQR, interquartile range.

Table 2. The baseline characteristics of ICC patients in the low TBS cohort who underwent OLR or LLR before and after PSM

Variables	Before PSM (n = 304)		p value	After PSM (n =140)		p value
	OLR (n = 236)	LLR (n = 68)		OLR (n = 93)	LLR (n = 47)	
Age, median (IQR), years	58.00 (50.00-65.00)	59.00 (50.25-66.00)	0.436	60.00 (51.50-67.50)	58.00 (50.0-66.00)	0.400
Gender			0.543			0.770
Female, n (%)	107 (45.3)	28 (41.2)		40 (43.0)	19 (40.4)	
Male, n (%)	129 (54.7)	40 (58.8)		53 (57.0)	28 (59.6)	
Short stature, median (IQR), m	1.63 (1.58-1.70)	1.63 (1.58-1.70)	0.775	1.65 (1.58-1.70)	1.63 (1.58-1.68)	0.757
Weight, median (IQR), Kg	61.00 (53.00-70.00)	64.00 (58.00-74.00)	**0.049**	61.19 (56.00-73.25)	63.00 (56.0-71.00)	0.522
BMI, median (IQR), kg/m^2	23.31 (20.76-25.75)	24.34 (21.93-26.35)	**0.020**	23.36 (20.76-25.92)	24.22 (21.9-25.97)	0.302
Hypertension, n (%)	58 (24.6)	21 (30.9)	0.296	24 (25.8)	14 (29.8)	0.617
Diabetes, n (%)	21 (8.9)	6 (8.8)	0.985	10 (10.8)	5 (10.6)	0.984
Alcohol, n (%)	43 (18.2)	19 (27.9)	0.080	17 (18.3)	13 (27.7)	0.201
HBV, n (%)	72 (30.5)	18 (26.5)	0.520	35 (37.6)	13 (27.7)	0.240
HCV, n (%)	3 (1.3)	1 (1.5)	0.899	0 (0)	0 (0)	-
WBC, median (IQR), 10^9/L	5.90 (4.88-7.15)	5.46 (3.91-6.75)	**0.019**	5.80 (4.76-6.79)	5.91 (4.72-7.16)	0.938
NE, median (IQR), 10^9/L	3.69 (2.88-4.69)	3.23 (2.25-4.32)	**0.019**	3.50 (2.71-4.30)	3.53 (2.48-4.47)	0.714
Lym, median (IQR), 10^9/L	1.54 (1.20-1.97)	1.58 (1.15-1.93)	0.591	1.57 (1.26-2.00)	1.65 (1.27-2.00)	0.817
NLR, median (IQR), %	2.29 (1.66-3.22)	2.27 (1.52-2.89)	0.156	2.20 (1.55-2.78)	2.10 (1.31-2.85)	0.616
PLT, median (IQR), 10^9/L	176.00 (128.00-223.00)	198.00 (147.00-238.00)	**0.044**	183.00 (128.43-234.00)	198.00 (138.00-236.00)	0.443
PLR, median (IQR), %	107.50 (82.69-147.72)	124.81 (90.05-168.57)	**0.046**	105.67 (80.55-148.60)	107.11 (87.5-153.77)	0.686
PT, median (IQR), s	1.02 (0.97-1.08)	1.03 (0.97-1.07)	0.924	1.03 (0.97-1.08)	1.03 (0.97-1.07)	0.725
INR, median (IQR), %	11.80 (11.20-12.60)	11.80 (11.10-12.80)	0.918	11.90 (11.20-12.65)	12.00 (11.2-13.00)	0.477
TB, median (IQR), μmol/L	14.96 (11.53-20.58)	16.02 (12.50-20.00)	0.666	14.90 (11.75-18.35)	16.74 (12.6-20.37)	0.119
ALT, median (IQR), U/L	26.00 (17.00-42.75)	23.00 (15.00-36.00)	0.136	24.00 (16.00-33.00)	23.00 (19.0-42.00)	0.632
AST, median (IQR), U/L	27.00 (21.25-38.00)	25.00 (20.00-33.00)	**0.042**	27.00 (21.50-34.50)	25.00 (20.0-34.00)	0.438
ALP, median (IQR), U/L	97.50 (78.25-152.00)	94.00 (75.00-114.00)	0.055	89.00 (74.00-117.00)	95.00 (71.0-117.00)	0.696
GGT, median (IQR), U/L	57.50 (27.00-169.50)	42.00 (25.00-74.00)	0.055	42.00 (24.50-107.00)	48.00 (30.0-84.00)	0.479
AFP, median (IQR), ng/mL	2.88 (1.94-4.39)	2.60 (1.88-5.01)	0.906	3.10 (2.01-5.52)	2.90 (1.90-5.01)	0.736
CA199, median (IQR), U/mL	50.77 (16.51-446.95)	28.03 (11.41-92.43)	**0.003**	28.09 (14.65-98.44)	30.36 (12.2-111.70)	0.935
CA125, median (IQR), U/ml	16.58 (9.08-45.84)	14.50 (7.93-19.30)	0.086	14.17 (8.87-30.87)	12.43 (7.25-18.38)	0.322
CEA, median (IQR), ng/mL	2.79 (1.61-5.01)	2.56 (1.38-4.36)	0.500	2.71 (1.63-4.64)	2.85 (1.44-4.42)	0.850
Child–Pugh, n (%)			0.121			0.774
A	216 (91.5)	66 (97.1)		88 (94.6)	45 (95.7)	
B	20 (8.5)	2 (2.9)		5 (5.4)	2 (4.3)	
Nerve invasion, n (%)	62 (26.3)	10 (14.7)	**0.048**	18 (19.4)	9 (19.1)	0.977

Data are presented as N (%) or median (IQR); Bold text hinted that these variables were statistically significant. because some cases could not simultaneously find effective matching objects, the matching result was not an absolute 1:3. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; LLR, laparoscopic liver resection; OLR, open liver resection; PSM, propensity score matching; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; WBC, white blood cells; NE, neutrophils; Lym, lymphocytes; NLR, neutrophil-to-lymphocyte ratio; PLT, platelets; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; AFP, alpha-fetoprotein; CA199, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; IQR, interquartile range.

Table 2. The baseline characteristics of ICC patients in the low TBS cohort who underwent OLR or LLR before and after PSM (continued)

Variables	Before PSM (n = 304)		p value	After PSM (n =140)		p value
	OLR (n = 236)	LLR (n = 68)		OLR (n = 93)	LLR (n = 47)	
Differentiation, n (%)			0.081			0.953
Poor	129 (54.7)	29 (42.6)		46 (49.5)	23 (48.9)	
Moderate / Well	107 (45.3)	39 (57.4)		47 (50.5)	24 (51.1)	
Satellite nodules, n (%)	17 (7.2)	5 (7.4)	0.967	6 (6.5)	4 (8.5)	0.655
Lymphatic metastasis, n (%)	50 (21.2)	5 (7.4)	**0.009**	8 (8.6)	4 (8.5)	0.985
Capsular invasion, n (%)	108 (45.8)	24 (35.3)	0.125	38 (40.9)	18 (38.3)	0.770
TNM, n (%)			**< 0.001**			0.717
I/II	121 (51.3)	52 (76.5)		68 (73.1)	33 (70.2)	
III/IV	115 (48.7)	16 (23.5)		25 (26.9)	14 (29.8)	
Adjuvant therapy, n (%)	80 (33.9)	13 (19.1)	**0.020**	28 (30.1)	9 (19.1)	0.165

Data are presented as N (%) or median (IQR); Bold text hinted that these variables were statistically significant. because some cases could not simultaneously find effective matching objects, the matching result was not an absolute 1:3. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; LLR, laparoscopic liver resection; OLR, open liver resection; PSM, propensity score matching; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; WBC, white blood cells; NE, neutrophils; Lym, lymphocytes; NLR, neutrophil-to-lymphocyte ratio; PLT, platelets; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; AFP, alpha-fetoprotein; CA199, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; IQR, interquartile range.

Table 3. The baseline characteristics of ICC patients in the high TBS cohort who underwent OLR or LLR before and after PSM

Variables	Before PSM (n = 322)		p value	After PSM (n = 88)		p value
	OLR (n = 263)	LLR (n = 59)		OLR (n = 57)	LLR (n = 31)	
Age, median (IQR), years	59.00 (51.00-65.00)	59.00 (49.00-68.00)	0.787	61.00 (51.00-64.50)	51.00 (48.00-66.00)	0.296
Gender			0.740			0.947
Female, n (%)	123 (46.8)	29 (49.2)		28 (49.1)	15 (48.4)	
Male, n (%)	140 (53.2)	30 (50.8)		29 (50.9)	16 (51.6)	
Short stature, median (IQR), m	1.63 (1.57-1.69)	1.62 (1.57-1.68)	0.788	1.61 (1.54-1.69)	1.63 (1.57-1.68)	0.501
Weight, median (IQR), Kg	60.00 (53.10-66.01)	65.00 (58.00-71.00)	**0.003**	62.00 (54.75-69.50)	64.00 (57.00-71.00)	0.458
BMI, median (IQR), kg/m^2	22.84 (20.84-24.88)	24.91 (21.91-27.34)	**< 0.001**	24.08 (21.75-26.51)	24.21 (22.07-26.42)	0.797
Hypertension, n (%)	59 (22.4)	13 (22.0)	0.947	10 (17.5)	6 (19.4)	0.833
Diabetes, n (%)	25 (9.5)	8 (13.6)	0.353	6 (10.5)	3 (9.7)	0.900
Alcohol, n (%)	60 (22.8)	17 (28.8)	0.329	15 (26.3)	8 (25.8)	0.959
HBV, n (%)	72 (27.4)	15 (25.4)	0.760	15 (26.3)	10 (32.3)	0.555

Data are presented as N (%) or median (IQR); Bold text hinted that these variables were statistically significant. because some cases could not simultaneously find effective matching objects, the matching result was not an absolute 1:3. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; LLR, laparoscopic liver resection; OLR, open liver resection; PSM, propensity score matching; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; WBC, white blood cells; NE, neutrophils; Lym, lymphocytes; NLR, neutrophil-to-lymphocyte ratio; PLT, platelets; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; AFP, alpha-fetoprotein; CA199, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; IQR, interquartile range.

Table 3. The baseline characteristics of ICC patients in the high TBS cohort who underwent OLR or LLR before and after PSM (continued)

Variables	Before PSM (*n* = 322)		*p* value	After PSM (*n* = 88)		*p* value
	OLR (*n* = 263)	LLR (*n* = 59)		OLR (*n* = 57)	LLR (*n* = 31)	
HCV, *n* (%)	0 (0)	0 (0)	-	0 (0)	0 (0)	-
WBC, median (IQR), 10^9/L	6.95 (5.64-8.16)	7.11 (5.65-8.77)	0.724	7.01 (5.80-7.98)	6.14 (4.87-7.71)	0.275
NE, median (IQR), 10^9/L	4.59 (3.65-5.75)	4.52 (3.60-6.03)	0.765	4.51 (3.41-5.54)	4.14 (2.77-5.34)	0.189
Lym, median (IQR), 10^9/L	1.51 (1.17-1.83)	1.61 (1.29-1.89)	0.098	1.59 (1.21-1.88)	1.62 (1.25-1.96)	0.878
NLR, median (IQR), %	3.08 (2.22-4.56)	2.55 (2.10-3.68)	0.066	2.82 (2.16-3.80)	2.41 (1.95-2.90)	0.088
PLT, median (IQR), 10^9/L	190.00 (143.00-241.00)	233.00 (187.00-292.00)	**< 0.001**	197.00 (154.00-245.50)	223.00 (182.00-280.00)	0.063
PLR, median (IQR), %	126.11 (91.93-180.45)	145.60 (102.38-190.27)	0.097	131.36 (93.89-166.49)	145.60 (96.79-171.26)	0.424
PT, median (IQR), s	1.02 (0.97-1.08)	1.00 (0.94-1.07)	0.224	1.01 (0.94-1.04)	0.98 (0.93-1.07)	0.813
INR, median (IQR), %	11.90 (11.20-12.90)	11.90 (11.00-12.70)	0.457	11.70 (11.00-12.75)	12.10 (10.90-13.00)	0.366
TB, median (IQR), μmol/L	13.60 (10.70-19.20)	11.50 (8.84-15.40)	**0.004**	13.40 (10.20-18.25)	10.90 (9.10-16.23)	0.085
ALT, median (IQR), U/L	25.00 (16.00-40.00)	19.00 (13.00-31.00)	**0.005**	23.00 (17.50-33.00)	20.00 (17.00-38.00)	0.717
AST, median (IQR), U/L	31.00 (24.00-43.00)	25.00 (21.00-31.00)	**< 0.001**	30.00 (23.00-35.00)	27.00 (24.00-38.00)	0.993
ALP, median (IQR), U/L	128.00 (99.00-191.00)	99.00 (81.00-122.00)	**< 0.001**	102.00 (84.00-125.50)	98.00 (85.00-120.00)	0.817
GGT, median (IQR), U/L	88.00 (48.00-185.00)	51.00 (33.00-82.00)	**< 0.001**	63.00 (38.50-100.50)	52.00 (34.00-98.00)	0.521
AFP, median (IQR), ng/mL	3.50 (2.24-7.01)	2.70 (1.72-4.74)	**0.018**	3.40 (2.15-5.38)	3.20 (1.76-5.90)	0.872
CA199, median (IQR), U/mL	105.10 (21.47-898.90)	54.86 (16.50-762.68)	0.431	86.87 (19.17-830.44)	55.51 (17.44-664.34)	0.972
CA125, median (IQR), U/ml	27.60 (11.66-94.97)	19.70 (9.58-44.67)	0.146	22.91 (7.91-84.84)	15.00 (6.42-31.73)	0.233
CEA, median (IQR), ng/mL	3.03 (1.59-7.60)	2.83 (1.66-9.39)	0.840	2.73 (1.41-4.41)	2.45 (0.96-10.00)	0.990
Child–Pugh, *n* (%)			0.741			0.920
A	244 (92.8)	54 (91.5)		53 (93.0)	29 (93.5)	
B	19 (7.2)	5 (8.5)		4 (7.0)	2 (6.5)	
Nerve invasion, *n* (%)	29 (11.0)	2 (3.4)	0.072	5 (8.8)	2 (6.5)	0.701
Differentiation, *n* (%)			0.073			0.349
Poor	154 (58.6)	27 (45.8)		28 (49.1)	12 (38.7)	
Moderate / Well	109 (41.4)	32 (54.2)		29 (50.9)	19 (61.3)	
Satellite nodules, *n* (%)	48 (18.3)	5 (8.5)	0.067	6 (10.5)	5 (16.1)	0.448
Lymphatic metastasis, *n* (%)	65 (24.7)	3 (5.1)	**0.001**	8 (14.0)	3 (9.7)	0.555
Capsular invasion, *n* (%)	165 (62.7)	29 (49.2)	0.054	31 (54.4)	18 (58.1)	0.740
TNM, *n* (%)			**< 0.001**			0.519
I/II	107 (40.7)	42 (71.2)		29 (50.9)	18 (58.1)	
III/IV	156 (59.3)	17 (28.8)		28 (49.1)	13 (41.9)	
Adjuvant therapy, *n* (%)	93 (35.4)	14 (23.7)	0.086	22 (38.6)	8 (25.8)	0.227

Data are presented as N (%) or median (IQR); Bold text hinted that these variables were statistically significant. because some cases could not simultaneously find effective matching objects, the matching result was not an absolute 1:3. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; LLR, laparoscopic liver resection; OLR, open liver resection; PSM, propensity score matching; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; WBC, white blood cells; NE, neutrophils; Lym, lymphocytes; NLR, neutrophil-to-lymphocyte ratio; PLT, platelets; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; AFP, alpha-fetoprotein; CA199, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; IQR, interquartile range.

Table 4. The surgical outcomes of ICC patients in the low TBS cohort who underwent OLR or LLR before and after PSM

Variables	Before PSM (n = 304)		p value	After PSM (n = 140)		p value
	OLR (n = 236)	LLR (n = 68)		OLR (n = 93)	LLR (n = 47)	
Operation time (IQR), min	242.50 (179.50-287.50)	187.50 (153.75-240.00)	**0.038**	215.00 (170.00-281.25)	180.00 (152.-230.00)	0.103
Blood loss (IQR), mL	200.00 (20.00-300.00)	75.00 (20.00-112.50)	**0.001**	125.00 (27.50-200.00)	100.00 (20.0-150.00)	**0.016**
CCI (IQR)	20.90 (8.70-22.60)	8.70 (8.70-22.60)	**0.047**	8.70 (8.70-22.60)	8.70 (8.70-22.60)	**0.017**
CD, n (%)	60 (25.4)	8 (11.7)	**0.017**	23 (24.7)	5 (10.6)	**0.049**
Lymph node dissection, n (%)	89 (37.7)	16 (23.5)	**0.030**	26 (27.9)	10 (21.2)	0.393
Waiting time for surgery (IQR), d	4.00 (3.00-6.00)	3.00 (3.00-5.00)	**0.043**	4.00 (3.00-5.00)	3.00 (2.25-4.75)	0.184
Postoperative discharge time (IQR), d	9.00 (7.00-11.00)	6.00 (5.00-8.00)	< 0.001	9.00 (7.00-11.00)	6.00 (5.00-9.00)	< 0.001

Data are presented as n (%) or median (IQR); Bold text hinted that these variables were statistically significant. because some cases could not simultaneously find effective matching objects, the matching result was not an absolute 1:3. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; LLR, laparoscopic liver resection; OLR, open liver resection; PSM, propensity score matching; CCI, charlson comorbidity index; CD, Clavien–Dindo ≥ III; IQR, interquartile range.

Table 5. The surgical outcomes of ICC patients in the high TBS cohort who underwent OLR or LLR before and after PSM

Variables	Before PSM (n = 322)		p value	After PSM (n = 88)		p value
	OLR (n = 263)	LLR (n = 59)		OLR (n = 57)	LLR (n = 31)	
Operation time (IQR), min	252.50 (181.25-313.75)	270.00 (180.00-345.00)	0.527	235.00 (177.50-337.50)	332.50 (257.50-422.50)	0.062
Blood loss (IQR), mL	300.00 (200.00-500.00)	100.00 (20.00-200.00)	**< 0.001**	325.00 (200.00-500.00)	100.00 (20.00-225.00)	**0.001**
CCI (IQR)	8.70 (8.70-22.60)	8.70 (8.70-19.13)	0.233	22.60 (8.70-25.10)	8.70 (8.70-12.18)	**0.035**
CD, n (%)	39 (14.8)	3 (5.0)	0.053	13 (22.8)	1 (3.2)	**0.016**
Lymph node dissection, n (%)	117 (44.4)	21 (35.5)	0.212	21 (36.8)	12 (38.7)	0.863
Length of hospital stay (IQR), d	14.00 (12.00-17.00)	10.00 (8.75-15.00)	**< 0.001**	12.50 (10.25-18.00)	11.00 (9.00-17.00)	0.127
Waiting time for surgery (IQR), d	4.00 (3.00-6.00)	4.00 (2.00-6.00)	0.658	4.00 (3.00-5.00)	5.00 (3.00-6.00)	0.322
Postoperative discharge time (IQR), d	9.00 (8.00-12.00)	6.50 (5.00-8.00)	**< 0.001**	10.00 (7.00-11.75)	7.00 (5.00-10.00)	**0.010**

Data are presented as n (%) or median (IQR); Bold text hinted that these variables were statistically significant. because some cases could not simultaneously find effective matching objects, the matching result was not an absolute 1:3. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; LLR, laparoscopic liver resection; OLR, open liver resection; PSM, propensity score matching; CCI, charlson comorbidity index; CD, Clavien–Dindo ≥ III; IQR, interquartile range.

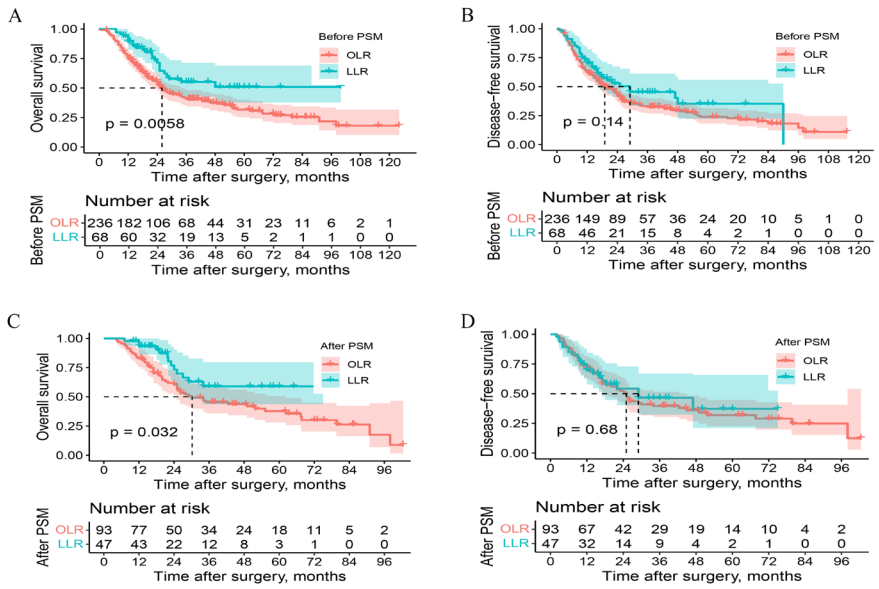

Figure 2. Kaplan–Meier curves estimating OS and DFS of ICC patients in the low TBS group before and after PSM. (A, B) OS and DFS of ICC patients who underwent LLR or OLR before PSM; **(C, D)** OS and RFS of ICC patients who underwent LLR or OLR after PSM. ICC, intrahepatic cholangiocarcinoma; PSM, propensity score matching; LLR, laparoscopic liver resection; OLR, open liver resection; OS, overall survival; DFS, disease-free survival.

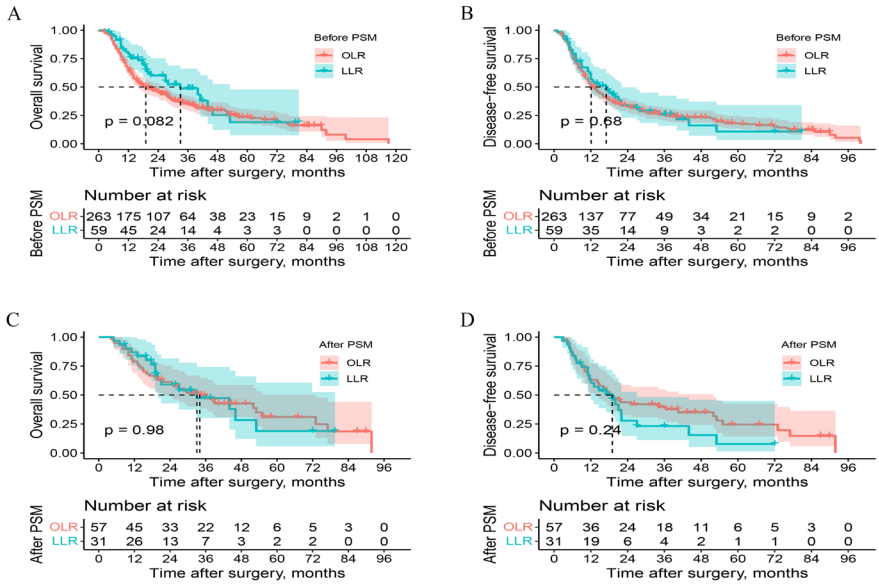

Figure 3. Kaplan–Meier curves estimating OS and DFS of ICC patients in the high TBS group before and after PSM. (A, B) OS and DFS of ICC patients who underwent LLR or OLR before PSM; **(C, D)** OS and RFS of ICC patients who underwent LLR or OLR after PSM. ICC, intrahepatic cholangiocarcinoma; PSM, propensity score matching; LLR, laparoscopic liver resection; OLR, open liver resection; OS, overall survival; DFS, disease-free survival.

5.1 percent; $p = 0.001$) and TNM stage (I/II: 40.7 *vs.* 71.2 percent; III/IV: 59.3 *vs.* 28.8 percent; $p < 0.001$). After PSM, the OLR group consisted of 31 patients, and the LLR group included 57 patients, with the disparities between the groups being effectively mitigated.

3.3. Perioperative outcomes between different surgical procedures in the low- and high-TBS groups

Table 4 provides the surgical outcomes in the low-TBS cohort. Before PSM, the operation time (242.50 *vs.* 187.50 min; $p = 0.038$), blood loss (200.00 *vs.* 75.00 mL; $p = 0.001$), waiting time for surgery (4.00 *vs.* 3.00 d; $p = 0.043$), incidence of CDc grade ≥ IIIa complications (25.4 *vs.* 11.7 percent, $p = 0.017$), CCI (20.9 *vs.* 8.70; $p = 0.047$), and postoperative discharge time (9.00 *vs.* 6.00 d; $p = 0.001$) were greater in the OLR group. After PSM,

LLR was still associated with less blood loss (125.00 *vs.* 100.00 mL; $p = 0.016$), lower CCI (8.7 *vs.* 8.7; $p = 0.017$), a decreased incidence rate of CDc grade ≥ IIIa complications (24.7 *vs.* 10.6 percent; $p = 0.049$) and a shorter postoperative discharge time (9.00 *vs.* 6.00 d; $p < 0.001$).

Table 5 presents the surgical outcomes in the high-TBS cohort. Before PSM, the LLR group presented reduced blood loss (300.00 *vs.* 100.00 mL; $p < 0.001$) and a shorter postoperative discharge time (9.00 *vs.* 6.50 d; $p = 0.010$). After PSM, the LLR group was associated with reduced blood loss (325.00 *vs.* 100.00 mL; $p = 0.001$), lower CCI (22.60 *vs*. 8.70; $p = 0.035$), a decreased incidence of CDc grade ≥ IIIa complications (22.8 *vs.* 3.2 percent; $p = 0.016$) and a shorter postoperative discharge time (10.00 *vs.* 7.00 d; $p = 0.010$).

3.4. Analysis of OS and RFS between different surgical procedures in the low- and high-TBS groups

Figure 2 shows a comparative analysis of the long-term outcomes among patients who underwent LLR and OLR in the low-TBS cohort. Before PSM, the results indicated that LLR exhibited superior OS, with LLR patients demonstrating higher OS rates at 1, 3, and 5 years than OLR patients (1 year: 94.1% *vs.* 77.9%; 3 years: 55.1%

Table 6. Univariable analysis and Multivariate Analysis for OS of ICC patients in the low TBS cohort after PSM

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age, years	0.997	0.976-1.018	0.753			
Gender, female *vs.* male	1.660	1.033-2.668	**0.036**	1.304	0.674-2.523	0.430
Short stature, m	0.070	0.004-1.158	0.063	0.343	0.008-15.163	0.580
Weight, Kg	0.987	0.967-1.006	0.180			
BMI, kg/m^2	0.988	0.925-1.055	0.709			
Hypertension	0.902	0.520-1.562	0.712			
Diabetes	0.453	0.165-1.244	0.124			
Alcohol	0.701	0.389-1.261	0.236			
HBV	1.015	0.618-1.668	0.953			
HCV	NA	NA	NA			
WBC, 10^9/L	1.029	0.902-1.175	0.670			
NE, 10^9/L	1.063	0.912-1.239	0.437			
Lym, 10^9/L	0.837	0.546-1.283	0.414			
NLR	1.043	0.977-1.114	0.208			
PLT, 10^9/L	1.002	0.999-1.006	0.132			
PLR,	1.004	1.000-1.008	**0.026**	1.002	0.997-1.006	0.499
PT, s	0.947	0.841-1.065	0.363			
INR	0.613	0.182-2.066	0.430			
TB, μmol/L	1.003	0.995-1.012	0.423			
ALT, U/L	1.004	1.000-1.007	0.069	1.002	0.997-1.007	0.362
AST, U/L	1.002	0.999-1.005	0.233			
ALP, U/L	1.004	1.001-1.006	**0.002**	1.003	0.999-1.007	0.199
GGT, U/L	1.002	1.000-1.004	**0.040**	0.999	0.996-1.002	0.638
AFP, ng/mL	0.999	0.996-1.002	0.389			
CA199, U/mL	1.001	1.000-1.002	0.056	1.000	1.000-1.001	0.349
CA125, U/mL	1.003	1.001-1.006	**0.006**	1.004	1.001-1.007	**0.003**
CEA, ng/mL	1.003	0.995-1.010	0.526			
Child–Pugh, A *vs.* B	0.930	0.335-2.581	0.890			
Nerve invasion	1.813	1.019-3.226	**0.043**	1.574	0.838-2.955	0.158
Differentiation, Poor *vs.* Moderate / Well	0.761	0.474-1.222	0.259			
Satellite nodules	1.536	0.661-3.571	0.319			
Lymph node dissection	1.163	0.670-2.020	0.591			
Lymphatic metastasis	3.287	1.602-6.747	**0.001**	3.081	1.394-6.808	**0.005**
Capsular invasion	0.916	0.560-1.496	0.726			
TNM, I/II *vs.* III/IV	0.892	0.514-1.549	0.686			
Surgical approach, LLR *vs.* OLR	0.522	0.284-0.959	**0.036**	0.445	0.235-0.843	**0.013**
Blood loss, ml	1.001	0.999-1.002	0.373			
CCI	1.007	0.974-1.041	0.678			
CD	0.550	0.281-1.077	0.081	1.154	0.532-2.500	0.717
Adjuvant therapy	1.045	0.625-1.747	0.868			

Bold text hinted that these variables were statistically significant. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; PSM, propensity score matching; ***OS***, overall survival; ***HR***, hazard ratio; ***CI***, confidence interval; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; WBC, white blood cells; NE, neutrophils; Lym, lymphocytes; NLR, neutrophil-to-lymphocyte ratio; PLT, platelets; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; AFP, alpha-fetoprotein; CA199, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; LLR, laparoscopic liver resection; OLR, open liver resection; CCI, charlson comorbidity index, CD, Clavien–Dindo ≥ III.

vs. 40.6%; 5 years: 50.9% *vs*. 31.7%, $p = 0.0058$). However, both groups presented similar DFS ($p = 0.14$). After PSM, the LLR group continued to have a better OS than the OLR group ($p = 0.032$), while DFS was comparable between the two groups. Notably, the median DFS time in the LLR group appeared to be longer than that in the OLR group (29 months *vs*. 25 months, $p = 0.068$).

In the high TBS cohort, Figure 3 shows that before PSM, the OS in the LLR group is comparable to that in the OLR group. However, the median survival time was seemingly superior in the LLR group than in the OLR group (33 months versus 19 months, $p = 0.082$), with no statistically significant difference in DFS between the two groups ($p = 0.68$). After PSM, there was no significant difference in OS ($p = 0.98$) or DFS ($p = 0.24$) between the two groups.

3.5. Univariable and multivariable Cox regression analyses of OS in the low- and high-TBS cohorts

Table 5 presents the results of Cox regression analysis exploring risk factors for OS in the low-TBS cohort. Univariate Cox regression analysis revealed that sex, PLR, ALP, γ-glutamyl transpeptidase (GGT), CA125, nerve invasion, lymphatic metastasis and surgical

Table 7. Univariable analysis and Multivariate Analysis for OS of ICC patients in the high TBS cohort after PSM

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age, years	1.010	0.986-1.034	0.434			
Gender, female *vs.* male	0.701	0.405-1.215	0.206			
Short stature, m	3.520	0.157-78.981	0.428			
Weight, Kg	1.005	0.982-1.029	0.660			
BMI, kg/m^2	1.008	0.925-1.098	0.855			
Hypertension	0.713	0.322-1.583	0.406			
Diabetes	1.288	0.546-3.039	0.563			
Alcohol	2.067	1.154-3.701	**0.015**	2.081	1.046-4.138	**0.037**
HBV	0.849	0.452-1.598	0.612			
HCV	NA	NA	NA			
WBC, 10^9/L	1.084	0.958-1.226	0.199			
NE, 10^9/L	1.143	0.993-1.314	0.062	0.989	0.779-1.257	0.931
Lym, 10^9/L	0.773	0.461-1.298	0.330			
NLR	1.128	0.981-1.297	0.090	1.049	0.820-1.342	0.705
PLT, 10^9/L	1.001	0.999-1.004	0.324			
PLR,	1.002	0.999-1.006	0.120			
PT, s	1.069	0.856-1.334	0.557			
INR	0.188	0.007-5.128	0.322			
TB, μmol/L	1.002	1.000-1.004	0.075	0.993	0.982-1.004	0.196
ALT, U/L	1.001	0.996-1.005	0.708			
AST, U/L	1.000	0.996-1.004	0.861			
ALP, U/L	1.003	1.000-1.005	**0.029**	1.003	0.993-1.013	0.581
GGT, U/L	1.006	1.002-1.010	**0.004**	1.000	0.991-1.009	0.951
AFP, ng/mL	1.000	0.998-1.002	0.706			
CA199, U/mL	1.001	1.000-1.001	**0.015**	1.001	1.000-1.001	0.150
CA125, U/mL	1.003	1.000-1.005	**0.016**	1.002	1.000-1.004	0.070
CEA, ng/mL	1.002	1.000-1.004	**0.027**	1.002	1.000-1.004	**0.044**
Child–Pugh, A *vs.* B	3.935	1.647-9.405	**0.002**	0.091	0.009-0.930	**0.043**
Nerve invasion	3.021	1.179-7.742	**0.021**	1.079	0.339-3.435	0.897
Differentiation, Poor *vs.* Moderate / Well	0.773	0.444-1.349	0.365			
Satellite nodules	1.632	0.793-3.357	0.183			
Lymph node dissection	0.978	0.561-1.706	0.937			
Lymphatic metastasis	1.762	0.824-3.769	0.144			
Capsular invasion	1.008	0.556-1.826	0.980			
TNM, I/II *vs.* III/IV	0.920	0.524-1.618	0.773			
Surgical approach, LLR *vs.* OLR	1.008	0.556-1.826	0.980			
Blood loss, mL	1.001	0.999-1.002	0.478			
CCI	0.988	0.954-1.023	0.508			
CD	0.914	0.445-1.879	0.808			
Adjuvant therapy	0.987	0.556-1.750	0.964			

Bold text hinted that these variables were statistically significant. ICC, intrahepatic cholangiocarcinoma; TBS, tumor burden score; PSM, propensity score matching; ***OS***, overall survival; ***HR***, hazard ratio; ***CI***, confidence interval; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; WBC, white blood cells; NE, neutrophils; Lym, lymphocytes; NLR, neutrophil-to-lymphocyte ratio; PLT, platelets; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; INR, international normalized ratio; TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; AFP, alpha-fetoprotein; CA199, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; LLR, laparoscopic liver resection; OLR, open liver resection; CCI, charlson comorbidity index, CD, Clavien–Dindo ≥ III.

approach were significantly associated with OS (all $p < 0.05$). Multivariate analysis confirmed that CA125 (HR: 1.004; 95% CI : 1.001–1.007; $p = 0.003$), lymphatic metastasis (HR: 3.081; 95% CI : 1.394–6.808; $p = 0.005$), and surgical approach (HR: 0.445; 95% CI : 0.235–0.843; $p = 0.013$) remained significantly correlated with OS.

Table 6 presents a detailed summary of the Cox regression analyses that were carried out to identify prognostic factors impacting OS in the high-TBS cohort. Univariate Cox regression analysis revealed that alcohol intake, ALP, GGT, CA199, CA125, CEA, Child–Pugh, and nerve invasion were linked to OS (all $p < 0.05$). Multivariate analysis confirmed that alcohol intake (HR: 2.081; 95% CI: 1.046-4.138; $p = 0.037$), CEA (HR: 1.002; 95% CI: 1.000-1.004; $p=0.044$), and Child–Pugh (HR: 0.091; 95% CI: 0.009-0.930; $p = 0.043$), continued to show significant associations with OS (Table 7).

4. Discussion

According to the guidelines of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), liver resection is indicated for patients with early-stage ICC (*20,21*). In recent years, LLR has been approved as a safe approach and has been applied for the treatment of many liver diseases. However, LLR is not recommended as a routine approach in the treatment of ICC according to the guidelines of AASLD and EASL. Moreover, the application of LLR in radical surgery for ICC lacks sufficient data, leading to uncertainty among clinicians regarding the selection of the optimal surgical procedure (*7*). Tumor size and number are important characteristics of solid tumors and are used in the selection of optimal treatment strategies (*22,23*). TBS, as a metric of tumor size and number, showed better efficacy in evaluating tumor burden and predicting long-term survival than tumor size and number (*11,14*).

In this study, through analyzing the clinical and follow-up data of 626 ICC patients from a multicenter database, several interesting findings were obtained. First, TBS, which is associated with poor tumor-related characteristics, may be a good indicator for predicting the long-term outcomes in ICC. Second, compared to OLR, LLR was associated with faster postoperative recovery. Third, patients with a low TBS grade (< 5.30) may benefit from LLR in terms of OS and DFS, while LLR could provide a comparable long-term survival for patients with a high TBS grade (> 5.30) compared to those who undergo OLR.

The number and size of tumors represent important morphologic considerations in the staging of ICC (*20,21*). Multiple foci of tumors may represent intrahepatic metastases, and tumor size is considered an important prognostic factor for ICC according to the latest AJCC staging system. Our previous study also revealed that tumor size was an independent risk factor for solitary ICC (*24*). Consequently, TBS may be helpful in capturing the tumor burden and predicting prognosis. For example, Moazzam *et al*. reported that TBS was an important prognostic factor for ICC and was associated with a higher risk of recurrence (*25*). In addition, Li *et al*. demonstrated that TBS could stratify ICC patients into different prognostic groups (*14*). In our study, ICC patients were stratified into two groups based on TBS. Obviously, there were significant differences between the two groups, including TNM stage, PLR and CA199, *etc*. Each of these factors was also an independent prognostic factor for ICC, which may lead to a poorer prognosis for ICC with high TBS grade. In fact, multivariate analysis still revealed that TBS was an independent risk factor for ICC. These findings suggest that TBS is an important prognostic factor for ICC and could be a good indicator for stratifying ICC patients into different groups.

Our results suggest that LLR is associated with faster postoperative recovery. Previous studies have shown that LLR was associated with less blood loss, a lower transfusion rate and a shorter postoperative hospital stay (*26-29*). However, these results focused mainly on the application of LLR in solitary ICC. For large or multiple ICCs, owing to the concerns of difficulty in achieving R0 resection and LND and tumor rupture (*30*), massive bleeding and tumor seeding, few studies have been conducted on this topic. In our study, after PSM, LLR remained related to less blood loss, lower CCI and shorter hospital stay in the high-TBS group. Several researchers have also reported that for large (≥ 5 cm) and multiple (≥ 2) ICCs, LLR could provide no worse short-term outcomes (*9*). These findings suggest that for treating ICC with high TBS grade, although LLR could be a complicated procedure, it remains a feasible and safe choice.

Our results further suggest that patients with a low TBS grade (< 5.30) may benefit from LLR in terms of OS and DFS, while LLR could provide a comparable long-term survival for patients with a high TBS grade (> 5.30) compared to those who undergo OLR. In the low-TBS group, survival analysis revealed that LLR had better OS than OLR before and after PSM. Indeed, in the Cox regression analysis, the surgical procedure was an independent prognostic factor for ICC. Several reasons could explain this issue: the low incidence rate of postoperative complications, the effective initiation of adjuvant therapies and the biologically favorable context provided by laparoscopy (*31,32*). In the high-TBS group, there were no statistically significant differences in OS or DFS between the LLR and OLR groups. These findings, together with those of other studies (*33*), lead us to conclude that LLR offers ICC patients a comparable and even better long-term prognosis than OLR, and this conclusion is more applicable in patients with low TBS scores.

One of the main concerns for LLR in treating ICC is the difficulty in performing LND. Indeed, the role

of LND for ICC remains controversial (*34,35*). Many previous studies urged surgeons to conduct LND as a routine procedure to provide accurate staging for ICC and improve survival. Consequently, routine LND is recommended by many experts and guidelines. However, some scholars argued against this because patients did not benefit from LND (*36*), which was also proven in our previous study (*37*). In this study, we found that more LND was performed in the high-TBS group, possibly because large or multiple ICCs were more likely to have positive lymph node status based on the preoperative imaging or intraoperative assessment. However, there was no significant difference in the rate of lymph node metastasis between the low- and high-TBS groups. In addition, there was no difference in the LND rate between the LLR and OLR groups in either the low or high TBS group after PSM. These findings are consistent with several studies (*38,39*). Furthermore, Ratti *et al*. revealed that for patients with biliary cancers, LND performed *via* a laparoscopic apparatus was associated with lower lymphadenectomy-related morbidity (*27*). These findings lead us to conclude that LND is no longer a hindrance to the application of LLR in treating ICC.

Multivariate Cox regression analysis was used to explore independent prognostic factors for ICC. Similar to the findings of previous studies, high CA125 and lymph node metastasis were poor prognostic factors in the low-TBS group (*40,41*), and patients with high CEA had significantly worse OS in the high-TBS group (*42*). Our finding that Child-Pugh class B score is a poor prognostic predictor is supported by many other studies (*43-45*). The Child–Pugh grade is used to evaluate the hepatic function reserve before treatment. However, recent studies revealed that a poorer hepatic reserve might lead to a deficiency of immune surveillance and defense by the liver; thus, the elimination of residual and migrating tumor cells by the immune system was impaired, which could cause tumor progression (*43,46,47*). Alcohol consumption was believed to be a risk factor for developing ICC (*48*), and it was identified to be a poor prognostic factor for ICC in the high-TBS group. However, the impact of alcohol consumption on the prognosis of individuals with this condition remains uncertain. Only a recent study revealed that it affected the prognosis of patients with recurrent ICC (*49*). Based on the findings in our study, reducing alcohol consumption was necessary to reduce the incidence and improve the prognosis of ICC.

Several limitations of the study warrant consideration. First, owing to its retrospective nature, selection bias was inherent, despite efforts to mitigate bias through 1:3 propensity score matching. Second, although TBS is an indicator that has high predictive ability, for multiple ICCs, it cannot reflect the influence of different locations on the long-term outcomes. Furthermore, the study cohort comprised solely individuals from China, thus potentially limiting the generalizability of the findings to populations with different living environments and habits. To enhance the broader applicability of the study results, external validation in diverse ethnic groups is recommended.

In conclusion, our study suggests that TBS is an important prognostic factor for ICC and could stratify ICC patients into groups with different survival outcomes. Compared with OLR, LLR is a safe and feasible option for treating ICC and is associated with faster postoperative recovery. Furthermore, patients with a low TBS grade (< 5.30) may benefit from LLR in terms of OS and DFS, while LLR could provide a comparable long-term outcome for patients with a high TBS grade (> 5.30) compared to those who undergo OLR.

Acknowledgements

We thank all the surgeons and other partners of the Department of Liver Transplantation and Hepatobiliary Surgery, Shandong Provincial Hospital Affiliated to Shandong First Medical University, the Department of Liver Surgery, West China Hospital and Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital of Zhengzhou University.

Funding: This study was supported by National Natural Science Foundation of China (No. 81373172, 81770646), Postdoctoral Research Foundation of China (No. 2021M702031), and Natural Science Foundation of Shandong Province (ZR2023QH063).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022; 72:7-33.
2. Beal EW, Tumin D, Moris D, Zhang XF, Chakedis J, Dilhoff M, Schmidt CM, Pawlik TM. Cohort contributions to trends in the incidence and mortality of intrahepatic cholangiocarcinoma. Hepatobiliary Surg Nutr. 2018; 7:270-276.
3. Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-year trends in cholangiocarcinoma incidence in the U.S.: Intrahepatic disease on the rise. Oncologist. 2016; 21:594-599.
4. Endo I, Gonen M, Yopp AC, *et al*. Intrahepatic cholangiocarcinoma: Rising frequency, improved survival, and determinants of outcome after resection. Ann Surg. 2008; 248:84-96.
5. Ciria R, Cherqui D, Geller DA, Briceno J, Wakabayashi G. Comparative short-term benefits of laparoscopic liver resection: 9000 cases and climbing. Ann Surg. 2016; 263:761-777.
6. Haber PK, Wabitsch S, Kästner A, Andreou A, Krenzien F, Schöning W, Pratschke J, Schmelzle M. Laparoscopic liver resection for intrahepatic cholangiocarcinoma: A single-center experience. . J Laparoendosc Adv Surg Tech A. 2020; 30:1354-1359.

7. Regmi P, Hu HJ, Paudyal P, Liu F, Ma WJ, Yin CH, Jin YW, Li FY. Is laparoscopic liver resection safe for intrahepatic cholangiocarcinoma? A meta-analysis. Eur J Surg Oncol. 2021; 47:979-989.
8. Wei F, Wang G, Ding J, Dou C, Yu T, Zhang C. Is it time to consider laparoscopic hepatectomy for intrahepatic cholangiocarcinoma? A meta-analysis. J Gastrointest Surg. 2020; 24:2244-2250.
9. Wei F, Lu C, Cai L, Yu H, Liang X, Cai X. Can laparoscopic liver resection provide a favorable option for patients with large or multiple intrahepatic cholangiocarcinomas? Surg Endosc. 2017; 31:3646-3655.
10. Uy BJ, Han HS, Yoon YS, Cho JY. Laparoscopic liver resection for intrahepatic cholangiocarcinoma. J Laparoendosc Adv Surg Tech A. 2015; 25:272-277.
11. Sasaki K, Morioka D, Conci S, Margonis GA, Sawada Y, Ruzzenente A, Kumamoto T, Iacono C, Andreatos N, Guglielmi A, Endo I, Pawlik TM. The tumor burden score: A new "Metro-ticket" prognostic tool for colorectal liver metastases based on tumor size and number of tumors. Ann Surg. 2018; 267:132-141.
12. Ho SY, Liu PH, Hsu CY, Ko CC, Huang YH, Su CW, Lee RC, Tsai PH, Hou MC, Huo TI. Tumor burden score as a new prognostic marker for patients with hepatocellular carcinoma undergoing transarterial chemoembolization. J Gastroenterol Hepatol. 2021; 36:3196-3203.
13. Elfadaly AN, Tsilimigras DI, Hyer JM, *et al.* Impact of tumor burden score on conditional survival after curative-intent resection for hepatocellular carcinoma: A multi-institutional analysis. World J Surg. 2021; 45:3438-3448.
14. Li H, Liu R, Qiu H, Huang Y, Liu W, Li J, Wu H, Wang G, Li D. Tumor burden score stratifies prognosis of patients with intrahepatic cholangiocarcinoma after hepatic resection: A retrospective, multi-Institutional study. Front Oncol. 2022; 12:829407.
15. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: A new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Cancer Res. 2004; 10:7252-7259.
16. Chen Q, Dai Z, Yin D, Yang LX, Wang Z, Xiao YS, Fan J, Zhou J. Negative impact of preoperative platelet-lymphocyte ratio on outcome after hepatic resection for intrahepatic cholangiocarcinoma. Medicine (Baltimore). 2015; 94:e574.
17. Chen Q, Yang LX, Li XD, Yin D, Shi SM, Chen EB, Yu L, Zhou ZJ, Zhou SL, Shi YH, Fan J, Zhou J, Dai Z. The elevated preoperative neutrophil-to-lymphocyte ratio predicts poor prognosis in intrahepatic cholangiocarcinoma patients undergoing hepatectomy. Tumour Biol. 2015; 36:5283-5289.
18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004; 240:205-213.
19. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: A novel continuous scale to measure surgical morbidity. Ann Surg. 2013; 258:1-7.
20. Bowlus CL, Arrivé L, Bergquist A, Deneau M, Forman L, Ilyas SI, Lunsford KE, Martinez M, Sapisochin G, Shroff R, Tabibian JH, Assis DN. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. Hepatology. 2023; 77:659-702.
21. European Association for the Study of the Liver. EASL-ILCA Clinical Practice Guidelines on the management of intrahepatic cholangiocarcinoma. J Hepatol. 2023; 79:181-208.
22. Gomez D, Cameron IC. Prognostic scores for colorectal liver metastasis: clinically important or an academic exercise? HPB (Oxford). 2010; 12:227-238.
23. Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, Alexander DD, Choti MA, Poston G. Survival after liver resection in metastatic colorectal cancer: Review and meta-analysis of prognostic factors. Clin Epidemiol. 2012; 4:283-301.
24. Kong J, Cao Y, Chai J, Liu X, Lin C, Wang J, Liu J. Effect of tumor size on long-term survival after resection for solitary intrahepatic cholangiocarcinoma. Front Oncol. 2021; 10:559911.
25. Moazzam Z, Alaimo L, Endo Y, *et al.* Combined tumor burden score and carbohydrate antigen 19-9 grading system to predict outcomes among patients with intrahepatic cholangiocarcinoma. J Am Coll Surg. 2023; 236:804-813.
26. Levi Sandri GB, Spoletini G, Mascianà G, Colasanti M, Lepiane P, Vennarecci G, D'Andrea V, Ettorre GM. The role of minimally invasive surgery in the treatment of cholangiocarcinoma. Eur J Surg Oncol. 2017; 43:1617-1621.
27. Ratti F, Cipriani F, Ariotti R, Gagliano A, Paganelli M, Catena M, Aldrighetti L. Safety and feasibility of laparoscopic liver resection with associated lymphadenectomy for intrahepatic cholangiocarcinoma: A propensity score-based case-matched analysis from a single institution. Surg Endosc. 2016; 30:1999-2010.
28. Takahashi M, Wakabayashi G, Nitta H, Takeda D, Hasegawa Y, Takahara T, Ito N. Pure laparoscopic right hepatectomy by anterior approach with hanging maneuver for large intrahepatic cholangiocarcinoma. Surg Endosc. 2013; 27:4732-4733.
29. Lee W, Park JH, Kim JY, Kwag SJ, Park T, Jeong SH, Ju YT, Jung EJ, Lee YJ, Hong SC, Choi SK, Jeong CY. Comparison of perioperative and oncologic outcomes between open and laparoscopic liver resection for intrahepatic cholangiocarcinoma. Surg Endosc. 2016; 30:4835-4840.
30. Martin SP, Drake J, Wach MM, Ruff S, Diggs LP, Wan JY, Brown ZJ, Ayabe RI, Glazer ES, Dickson PV, Davis JL, Deneve JL, Hernandez JM. Laparoscopic approach to intrahepatic cholangiocarcinoma is associated with an exacerbation of inadequate nodal staging. Ann Surg Oncol. 2019; 26:1851-1857.
31. Chana P, Burns EM, Arora S, Darzi AW, Faiz OD. A systematic review of the impact of dedicated emergency surgical services on patient outcomes. Ann Surg. 2016; 263:20-27.
32. Ratti F, Maina C, Clocchiatti L, Marino R, Pedica F, Casadei Gardini A, De Cobelli F, Aldrighetti LAM. Minimally invasive approach provides oncological benefit in patients with high risk of very early recurrence (VER) after surgery for intrahepatic cholangiocarcinoma (iCCA). Ann Surg Oncol. 2024; 31:2557-2567.
33. Guerrini GP, Esposito G, Tarantino G, Serra V, Olivieri T, Catellani B, Assirati G, Guidetti C, Ballarin R, Magistri P, Di Benedetto F. Laparoscopic versus open liver resection for intrahepatic cholangiocarcinoma: The first meta-analysis. Langenbecks Arch Surg. 2020; 405:265-275.
34. Choi SB, Kim KS, Choi JY, Park SW, Choi JS, Lee WJ, Chung JB. The prognosis and survival outcome

of intrahepatic cholangiocarcinoma following surgical resection: association of lymph node metastasis and lymph node dissection with survival. Ann Surg Oncol. 2009; 16:3048-3056.
35. Li DY, Zhang HB, Yang N, Quan Y, Yang GS. Routine lymph node dissection may be not suitable for all intrahepatic cholangiocarcinoma patients: results of a monocentric series. World J Gastroenterol. 2013; 19:9084-9091.
36. Shimada M, Yamashita Y, Aishima S, Shirabe K, Takenaka K, Sugimachi K. Value of lymph node dissection during resection of intrahepatic cholangiocarcinoma. Br J Surg. 2001; 88:1463-1466.
37. Li F, Jiang Y, Jiang L, Li Q, Yan X, Huang S, Chen J, Yuan S, Fu Y, Liu J. Effect of lymph node resection on prognosis of resectable intrahepatic cholangiocarcinoma: A systematic review and meta-analysis. Front Oncol. 2022; 12:957792.
38. Ratti F, Fiorentini G, Cipriani F, Paganelli M, Catena M, Aldrighetti L. Perioperative and long-term outcomes of laparoscopic versus open lymphadenectomy for biliary tumors: A propensity-score-based, case-matched analysis. Ann Surg Oncol. 2019; 26:564-575.
39. Yoon YS, Han HS, Cho JY, Choi Y, Lee W, Jang JY, Choi H. Is laparoscopy contraindicated for gallbladder cancer? A 10-year prospective cohort study. J Am Coll Surg. 2015; 221:847-853.
40. Higashi M, Yamada N, Yokoyama S, Kitamoto S, Tabata K, Koriyama C, Batra SK, Yonezawa S. Pathobiological implications of MUC16/CA125 expression in intrahepatic cholangiocarcinoma-mass forming type. Pathobiology. 2012; 79:101-106.
41. Guglielmi A, Ruzzenente A, Campagnaro T, Valdegamberi A, Bagante F, Bertuzzo F, Conci S, Iacono C. Patterns and prognostic significance of lymph node dissection for surgical treatment of perihilar and intrahepatic cholangiocarcinoma. J Gastrointest Surg. 2013; 17:1917-1928.
42. Moro A, Mehta R, Sahara K, *et al.* The impact of preoperative CA19-9 and CEA on outcomes of patients with intrahepatic cholangiocarcinoma. Ann Surg Oncol. 2020; 27:2888-2901.
43. Zhang K, Yu J, Yu X, Han Z, Cheng Z, Liu F, Liang P. Clinical and survival outcomes of percutaneous microwave ablation for intrahepatic cholangiocarcinoma. Int J Hyperthermia. 2018; 34:292-297.
44. Nishikawa H, Nishijima N, Enomoto H, Sakamoto A, Nasu A, Komekado H, Nishimura T, Kita R, Kimura T, Iijima H, Nishiguchi S, Osaki Y. Predictive factors in patients with hepatocellular carcinoma receiving sorafenib therapy using time-dependent receiver operating characteristic analysis. J Cancer. 2017; 8:378-387.
45. Lee S, Kim BK, Kim SU, Park SY, Kim JK, Lee HW, Park JY, Kim DY, Ahn SH, Tak WY, Kweon YO, Lee JI, Lee KS, Kim HJ, Han KH. Clinical outcomes and prognostic factors of patients with advanced hepatocellular carcinoma treated with sorafenib as first-line therapy: A Korean multicenter study. J Gastroenterol Hepatol. 2014; 29:1463-1469.
46. Racanelli V, Rehermann B. The liver as an immunological organ. Hepatology. 2006; 43:S54-S62.
47. Jenne CN, Kubes P. Immune surveillance by the liver. Nature Immunology. 2013; 14:996-1006.
48. Petrick JL, Campbell PT, Koshiol J, *et al.* Tobacco, alcohol use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: The Liver Cancer Pooling Project. Br J Cancer. 2018; 118:1005-1012.
49. Yuan ZB, Fang HB, Feng QK, Li T, Li J. Prognostic factors of recurrent intrahepatic cholangiocarcinoma after hepatectomy: A retrospective study. World J Gastroenterol. 2022; 28:1574-1587.

Received September 6, 2024; Revised October 16, 2024; Accepted November 21, 2024.

**Address correspondence to:*
Jun Liu and Guangbing Li, Department of Liver Transplantation and Hepatobiliary Surgery, Shandong Provincial Hospital Affiliated to Shandong First Medical University, No.324, Jingwu Road, Ji'nan, Shandong 250021, China.
E-mail: dr_liujun1967@126.com (JL), lgb002@126.com (GL)

Released online in J-STAGE as advance publication December 12, 2024.