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Outcomes of pure laparoscopic Glissonian pedicle approach hepatectomy for hepatocellular carcinoma: a propensity score matching analysis

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Abstract

Background Few studies had been performed to concern the outcomes of pure laparoscopic Glissonian pedicle approach hepatectomy (LGAH) for hepatocellular carcinoma (HCC). The aim of this study was to compare the outcomes of LGAH versus open Glissonian pedicle approach hepatectomy (OGAH) for HCC, especially in patients with cirrhosis.

Methods Hepatocellular carcinoma patients who underwent pure LGAH and OGAH between January 2015 and July 2017 in our institution were retrospectively enrolled in this study. Propensity score matching (PSM) of patients in a ratio of 1:1 was conducted to adjust the known confounders. The perioperative and oncological outcomes were compared between the two groups after PSM.

Results Some 80 patients underwent pure LGAH and 134 had OGAH. After PSM, 67 patients in each group were well matched for analysis. Both the postoperative overall complication rates (13.4% vs. 29.9%, $P=0.021$) and mean comprehensive complication index (2.63 vs. 7.40, $P=0.035$) were significantly lower in the LGAH group than those in OGAH group. Although the operative time was longer in the LRH group ($P<0.001$), the length of postoperative hospital stay was shorter in the LRH group ($P=0.024$). Furthermore, both the 3-year overall survival rate (73.3% for LGAH vs. 77.8% for OGAH, $P=0.338$) and 3-year disease-free survival rate (56.4% for LGAH vs. 62.5% for OGAH, $P=0.455$) were not significantly different between the groups.

Conclusion Pure laparoscopic Glissonian approach may be a better alternative to open Glissonian approach in selected HCC patients, which provided fewer complications, shorter postoperative hospital stay and comparable oncological outcomes.

Keywords Laparoscopic hepatectomy · Open hepatectomy · Glissonian approach · Hepatocellular carcinoma

In recent years, significant advances have been made in laparoscopic hepatectomy (LH) because of advancements in the design of laparoscopic surgical instruments and improvements in surgical techniques. Firstly, the total number of LH has rapidly increased, from 2804 cases to more than 9500 cases [1]. Secondly, the indications for laparoscopic liver surgery, which was originally used mainly for diagnostic procedures [2], has now expanded to include benign and malignant tumors of the liver [3] and even donor hepatectomies [4, 5]. Moreover, the proportion of LH being performed for malignancies has increased from 50% at the time of the first international consensus to the current rate of 65% after the second international consensus [6]. Thirdly, some important techniques of open liver resection could be safely performed laparoscopically, including anterior approach hepatectomy, anatomical hepatectomy, selective hemihepatic inflow occlusion, and the Glissonian pedicle approach hepatectomy [7–10].

The Glissonian pedicle approach, described as the extrahepatic control of Glisson's pedicle, was first introduced by Lortat-Jacob et al. as an alternative method of full inflow

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control of the liver [11]. The Glissonian pedicle approach to open liver resection, including extrahepatic control of Glisson's pedicle and *en bloc* stapling transection of the portal triad, was pioneered by Launois [12], Takasaki [13], and Galperin et al. [14] which had a lot of advantages. Previous literatures such as [15, 16] revealed that the Glissonian pedicle approach can reduce the portal triad closure time and reduce intraoperative hemorrhage. Furthermore, a randomized controlled trial [17] reported that the Glissonian pedicle approach was faster than hilar dissection. In addition, another retrospective study demonstrated that the open Glissonian pedicle approach hepatectomy was an independent prognostic indicator for survival over the standard approach in patients with hepatocellular carcinoma (HCC) [18].

With the development of laparoscopic liver resection, the Glissonian pedicle approach has been increasingly proposed as a safe and efficient method for laparoscopic liver surgery. For instance, Machado et al. [19, 20] have demonstrated the feasibility and safety of the intrahepatic Glissonian approach for laparoscopic liver resection. Meanwhile, Cho and colleagues [21] reported that the extrahepatic Glissonean approach was also feasible and safe for laparoscopic anatomical resection of the liver. Recently, Machado et al. [10] performed a 7-year observational study and found that intrahepatic Glissonian approach had several advantages over standard LH including shorter operative time, lower transfusion rates, and fewer overall complications. However, the previous studies were mainly focused on the technical feasibility of the Glissonian approach for laparoscopic liver resection, in which the perioperative and oncological outcomes were rarely noticed. To our knowledge, no systematic study has directly compared the perioperative and oncological outcomes of laparoscopic Glissonian pedicle approach hepatectomy (LGAH) with open Glissonian pedicle approach hepatectomy (OGAH) for HCC. Nevertheless, the traditional OGAH remains the classic procedure for HCC at present. It remains unclear how technical changes associated with LGAH of HCC affect surgical efficacy and oncologic outcomes when compared with traditional procedures. Therefore, we performed this study to compare the outcomes of LGAH versus OGAH for HCC in a high-volume HPB center using the propensity score matching (PSM) method.

Materials and methods

Patients and data

The data of HCC patients who underwent Glissonian pedicle approach liver resection in West China Hospital of Sichuan Univeristy between January 2015 and July 2017 were retrospectively collected from a prospectively established database. Our selection criteria for patients in this study included (1) patients aged 18–75 years, (2) liver function classified as Child-Pugh class A or B, (3) histologically confirmed HCC from postoperative pathological examination and tumor $\leq$ 10 cm, and (4) patients underwent anatomical hepatectomy. The Contraindication were as follows: (1) HCC involve the major vascular or the hilum; (2) HCC invaded the diaphragm or other surrounding tissue; (3) patients who needed reconstruction of vessels or bile ducts; (4) the presence of a known portal vein or bile duct anatomic variations; (5) a retention rate of preoperative indocyanine green 15 min (ICG-R15) > 15%, and a residual liver volume as a percentage of standard liver volume < 40%. Both the LGAH and OGAH methods were applicable for these patients, and the operative programme was voluntarily chosen by these patients after being fully informed of the advantages and disadvantages of the two operation methods.

Therapeutic regimen for all patients and all operations were performed by the same surgical team. The preoperative evaluation was similar for LGAH and OGAH procedures and included blood examinations, chest X-ray, electrocardiography, abdominal ultrasound, and contrast computed tomography scan (CT)/enhanced magnetic resonance imaging(MRI). The preoperative three-dimensional reconstruction CT/MRI were also performed when considering the Glissonian approach. In cases with age more than 65 years old, we performed spirometry and echocardiography. Liver function was assessed by both the Child-Pugh grading and preoperative ICG clearance test. Laboratory blood tests included blood routine, conventional coagulation examinations, alanine aminotransferase (ALT), aspartate transaminase (AST), serum total bilirubin (TBIL), albumin (Alb), serum alpha-fetoprotein (AFP). The primary endpoints were overall survival (OS), disease-free survival (DFS) and postoperative morbidity. The secondary endpoints included the total operation time, the need of Pringle maneuver (15 min clamping and 5 min release), the duration of inflow occlusion, the need of blood transfusion and postoperative hospital stay. Informed consents were obtained according to the Declaration of Helsinki. A written informed consent was obtained from each subject involved in the study. The study was approved by the Ethics Committee of Sichuan University.

Surgical procedure

Our detailed technique for LH had been previously described [22, 23]. Briefly, after pneumoperitoneum was established and exposure obtained, laparoscopic ultrasound was used to identify the lesion and guide resection in all cases. The Pringle's maneuver technique was always prepared for controlling the hepatic inflow by a tourniquet, which was used intermittently as necessary. After mobilization of the liver, the corresponding Glissonean pedicle was encircled by using the method of Cho et al. [21]

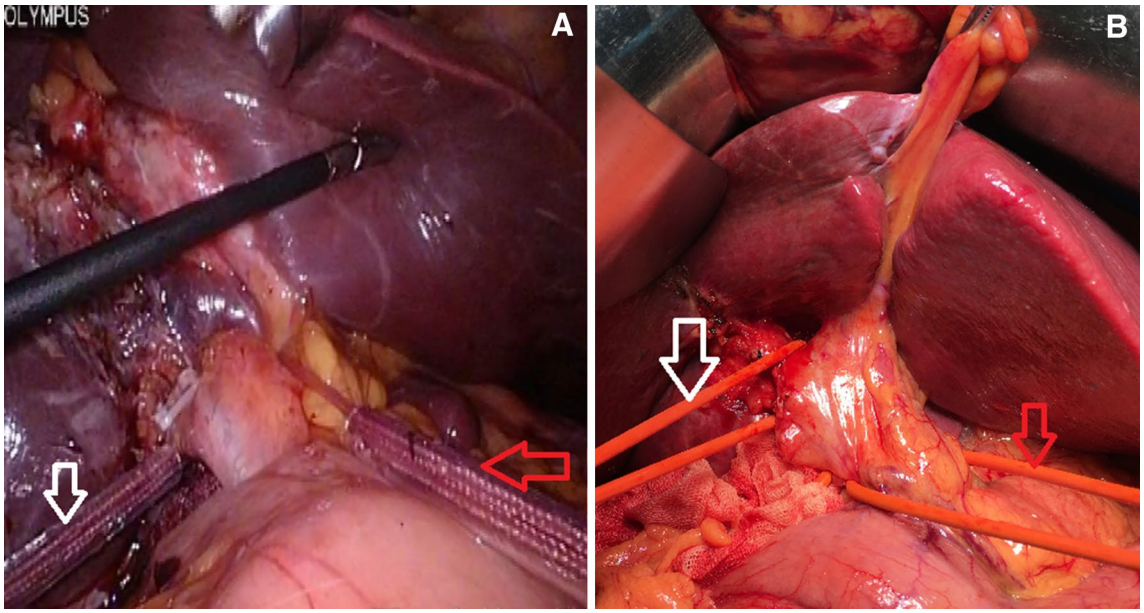

Fig. 1 Early isolation and taping of the Glissonean pedicle. **A** The right and left Glissonian pedicles were encircled laparoscopically. white arrow, right Glissonian pedicle; red arrow, left Glissonian pedicle. **B** The right Glissonian pedicle was encircled by a 12 Fr urethral catheter in a case of open right hemihepatectomy. white arrow, right Glissonian pedicle; red arrow, the Pringle maneuver. (Color figure online)

(Fig. 1A). However, we did not transect the Glissonean pedicle before the sufficient parenchyma dissection is done as described by Lee et al. [24]. We marked the ischemic line with electrocautery on the liver capsule after the corresponding Glissonean pedicle was occluded. The superficial parenchyma was dissected by harmonic scalpel (Ethicon Endo-Surgery, USA) along the demarcation line, while the deeper tissue was dissected by laparoscopic cavitron ultrasonic surgical aspirator (CUSA, Valleylab, Inc, USA) or Ligasure (ValleyLab, Inc, USA) [23]. In order to avoid dissemination of the mallignant tumor cells and decrease the blood loss, the corresponding Glissonean pedicle was continuously clamped during parenchyma dissection. Intraparenchymal vascular and biliary structures, which were larger than 5 mm, were dissected and clamped by Hem-o-lok clips or Titanium clips. After sufficient parenchymal dissection was done so that the whole bifurcating Glissonian pedicle was exposed, the hepatic pedicle tissue was transected by a laparoscopic linear stapler with 60 mm blue cartridge (Endopath Endocutter; Ethicon Endosurgery). It is noteworthy that stapling was done while the tape was retracted toward the contralateral side which prevented injury or stricture of the contralateral Glissonian pedicle branch. The remnant liver parenchyma is resected with or without the transection of main hepatic vein by the linear stapler and hepatectomy finished. If hemostasis on the remnant liver surface was inadequate, the BiClamp (VIO 300D system, ERBE, Germany) was used for further hemostasis.

In the OGAH group, patients under the general anesthesia were placed in supine position and the laparotomy was performed through an reverse L-incision or a right subcostal incision. Ultrasound examination was also performed to reconfirm the location and size of the tumor and guide resection in all cases. The Pringle's maneuver technique was routinely prepared for controlling the hepatic inflow and the corresponding Glissonean pedicle was encircled by a 12 Fr urethral catheter (Fig. 1B). The same surgical procedures for LGAH group were used to the OGAH group. The slight difference was that CUSA plus bipolar coagulation or clamp crushing plus bipolar coagulation were used as the main methods for parenchyma transection in the OGAH group. Similarly, stapling is done while the tape is retracted toward the contralateral side.

For both the LGAH and OGAH groups, the central venous pressure (CVP) were kept below 5 mmHg during liver parenchymal transection as recommended in the literature [25]. In order to achieve this goal, a single anesthesia team experienced in liver resection, especially in low CVP anesthesia, was involved in all cases, which enabled performance of each case under a CVP maintained between 0 and 5 mm Hg.

Postoperative management and follow up

Patients in the two groups received the same postoperative care by the same team of surgeons. Postoperative blood routine and hepatic function testing which included serum TBIL, ALT, AST, and Alb were performed on postoperative days (POD)s 1, 3, 5, and 7 (if the patient did not discharge at POD 7). The abdominal ultrasound examination was repeated on POD 5. Abdominal drainage was removed when ultrasound showed no abnormal findings and the drainage fluid without bile leakage. All patients were followed up with a standardized follow-up protocol. Blood routine and hepatic function testing, assessment of serum AFP levels, and testing for HBV-DNA load were required bimonthly in the first postoperative year, and then quarterly if no recurrence was detected. Abdominal enhanced CT was performed 1 month after the operation and quarterly in the first year, and half-yearly afterwards. Recurrence was defined as the appearance of new lesions with HCC-characterisitc findings on follow up CT or MRI.

Definitions

Liver resections were defined according to the Brisbane 2000 classification [26]. A minor resection is one in which two or fewer Couinaud segments are removed, while a major resection is one in which three or more segments are removed. Postoperative morbidities were classified according to the Clavien-Dindo classification [27] and the comprehensive complication index (CCI) [28] were also used to describe overall morbidity. Postoperative mortality was defined as event occurring during the first 90 days after the operation. Hemorrhage was identified as a drop in hemoglobin level > 3 g/dl post-operatively compared with the post-operative baseline level and/or any post-operative transfusion of packed red blood cells for a falling hemoglobin [29]. Biliary leakage was defined as a bilirubin concentration in drain fluid at least three times the serum bilirubin level on or after postoperative day 3 [30]. Postoperative ascites was defined by an abdominal drainage output more than 500 mL/day, or required treatment to be controlled [31]. Posthepatectomy liver failure was defined according to the International Study Group of Liver Surgery [32].

Statistical analysis

Continuous variables with a normal distribution were expressed as mean standard deviation and compared using two-sided Student's *t* tests. Continuous variables that were not normally distributed are reported as median (range) values and comparison of this kind of data was achieved by Mann–Whitney *U* test and Wilcoxon rank sum test before and after PSM, respectively. And the pearson ^{2} test or the Fisher's exact test was appropriate for categorical data according to the numbers obtained. OS and RFS were analyzed according to the Kaplan–Meier estimate. To eliminate possible selection bias, the propensity score (PS) analysis model was used. A PS matching ratio 1:1 was achieved based on the "nearest neighbor" method [33]. The PS was estimated using logistic regression which included the following variables: age, sex, body mass index(BMI), American Society of Anesthesiologists (ASA) grade, HBV carrier status, HCV carrier status, Child-Pugh class, comorbid disease, background cirrhosis, preoperative level of AFP, preoperative level of ICG-R15, type of resection, previous upper abdominal surgery and tumor characteristics (size, number). Survival curves were compared between the PS-matched groups using the log-rank test. All calculations were performed using the SPSS 22.0 statistical software. A P value of < 0.05 was considered as statistically significant.

Results

Patient characteristics

Between January 2015 and July 2017, a total of 214 HCC patients underwent Glissonian approach liver resection in which 80 patients underwent LGAH and 134 had OGAH. The patients' baseline characteristics in groups were shown in Table 1. The two groups were similar in terms of age, sex, BMI, HBV carrier status, HCV carrier status, background cirrhosis, Child-Pugh class, comorbid disease, Preoperative AFP, Preoperative ICG-R15, type of resection, and the number of tumors. However, ASA grade, previous upper abdominal surgery and tumour size were different between the groups. After PSM, 67 patients were included in each group (Table 2). Both groups were well matched, including the ASA grade, previous upper abdominal surgery and tumour size.

Operation and postoperative outcomes

The Glissonian pedicle approach hepatectomy was successfully performed in all of the patients. However, conversion to open surgery was required in two patients (conversion rate: 2.9%) in the LGAH group. One patient eventually needed conversion to open surgery due to difficulty in stopping parenchymal hemorrhage laparoscopically, and the other one due to right hepatic vein injury. Table 3 summarizes the operation and postoperative outcomes of both groups after PS matching. The Glissonian approach liver resection had been applied to different types of hepatectomies in the groups which included right hepatectomy, left hepatectomy, left lateral sectionectomy, right posterior sectionectomy, right anterior sectionectomy, central hepatectomy, and

Table 1 Patients' baseline and tumour characteristics before propensity score matching

	Laparoscopic group ($n=80$)	Open group ($n=134$)	P value
Age, mean (SD)	54.54 ± 11.38	52.49 ± 12.65	0.235[a]
Sex, M:F	71:9	118:16	0.879[c]
BMI,mean (SD)	23.41 ± 2.32	22.79 ± 2.51	0.076[a]
HBV carrier, *n* (%)	63 (78.8)	113 (84.3)	0.302[c]
HCV carrier, *n* (%)	1 (1.2)	2 (1.5)	1.000[b]
Liver cirrhosis, *n* (%)	52 (65.0)	86 (64.2)	0.903[c]
Child-Pugh class, *n* (%)			1.000[b]
A	78 (97.5)	131 (97.8)	
B	2 (2.5)	3 (2.2)	
ASA grade, *n* (%)			0.000[c]
I/II	77 (96.2)	87 (64.9)	
III/IV	3 (3.8)	47 (35.1)	
Comorbid disease, *n* (%)	16 (20.0)	41 (30.6)	0.090[c]
HTN	8 (10.0)	24 (17.9)	
DM	5 (6.2)	20 (14.9)	
COPD	3 (3.8)	4 (3.0)	
Preoperative AFP, *n* (%)			0.090[c]
Increased (≥ 400 ng/mL)	27 (33.8)	61 (45.5)	
Not increased (< 400 ng/mL)	53 (66.2)	73 (54.5)	
TB (μmol/L), mean (SD)	15.29 ± 5.66	14.64 ± 7.05	0.489[a]
ALB (g/L), mean (SD)	41.78 ± 3.42	41.38 ± 4.27	0.483[a]
AST (IU/L), mean (SD)	51.05 ± 48.89	48.19 ± 33.11	0.611[a]
ALT (IU/L), mean (SD)	53.75 ± 55.60	51.61 ± 32.33	0.722[a]
Preoperative ICG-R15(%), mean (SD)	6.36 ± 2.56	6.58 ± 2.35	0.513[a]
Type of resection, *n* (%)			0.289[c]
Major	40 (50.0)	77 (57.5)	
Minor	40 (50.0)	57 (42.5)	
Previous upper abdominal surgery, *n* (%)	4 (5.0)	22 (16.4)	0.013[c]
Tumor size (cm), mean (SD)	4.94 ± 2.60	5.82 ± 2.34	0.011[a]
Number of tumors, *n* (%)			0.571[c]
Solitary	67 (83.8)	116 (86.6)	
Multiple	13 (16.2)	18 (13.4)	

AFP alpha-feto-protein, *ALB* albumin, *ALT* alanine transaminase, *ASA* American Society of Anesthesiologists, *AST* aspartate transaminase, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *F* female, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HTN* hypertension, *ICG* indocyanine green, *M* male, *SD* standard deviation, *TB* total bilirubin

[a]Student's test

[b]Fisher exact test

[c]Pearson χ^2 test

extended left hepatectomy. There were no significant differences in the types of liver resection between the two groups. However, both the duration of operation and the clamping time with Pringle maneuver were significantly longer in the LGAH group than in the OGAH group (255.8 vs. 201.5 min, $P<0.001$; and 50.3 vs. 35.5 min, $P=0.001$, respectively). Nevertheless, the need of Pringle maneuver was not significant different between both groups. Moreover, there were no significant differences between the groups regarding intraoperative blood loss or blood transfusion.

One in-hospital death was recorded in the OGAH group on POD 10 owing to pulmonary embolism on POD 4 and secondary multiple organ failure. The most common complications for the both groups were similar, including ascites, pleural effusion, and pneumonia. In the LGAH group, 9 of 67 patients (13.4%) had a complication, compared with 20 of 67 (29.9%) in the OGAH group. Both the postoperative overall complication rates (13.4% vs. 29.9%, $P=0.021$) and mean CCI (2.63 vs. 7.40, $P=0.035$) were significantly lower in the LGAH

Table 2 Patients' baseline and tumor characteristics after propensity score matching

	Laparoscopic group ($n=67$)	Open group ($n=67$)	P value
Age, mean (SD)	54.28 ± 12.03	53.06 ± 13.42	0.579[a]
Sex, M:F	59:8	57:10	0.612[c]
BMI, mean (SD)	23.28 ± 2.36	22.94 ± 2.89	0.463[a]
HBV carrier, *n* (%)	54 (80.6)	55 (82.1)	0.825[c]
HCV carrier, *n* (%)	0 (0.0)	0 (0.0)	–
Liver cirrhosis, *n* (%)	45 (67.2)	41 (61.2)	0.471[c]
Child-Pugh class, *n* (%)			1.000[b]
A	66 (98.5)	65 (97.0)	
B	1 (1.5)	2 (3.0)	
ASA grade, *n* (%)			1.000[b]
I/II	64 (95.5)	64 (95.5)	
III/IV	3 (4.5)	3 (4.5)	
Comorbid disease, *n* (%)	15 (22.4)	16 (23.9)	0.838[c]
HTN	7 (10.4)	9 (13.4)	
DM	5 (7.5)	7 (10.4)	
COPD	3 (4.5)	2 (3.0)	
Preoperative AFP, *n* (%)			0.858[c]
Increased (≥ 400 ng/mL)	25 (37.3)	24 (35.8)	
Not increased (< 400 ng/mL)	42 (62.7)	43 (64.2)	
TB (μmol/L), mean (SD)	15.01 ± 5.49	14.64 ± 5.67	0.697[a]
ALB (g/L), mean (SD)	41.79 ± 3.39	41.96 ± 4.01	0.791[a]
AST (IU/L), mean (SD)	52.82 ± 52.99	47.18 ± 37.85	0.479[a]
ALT (IU/L), mean (SD)	56.31 ± 60.09	48.76 ± 29.69	0.358[a]
Preoperative ICG-R15 (%), mean (SD)	6.42 ± 2.48	6.36 ± 2.56	0.902[a]
Type of resection, *n* (%)			1.000[c]
Major	37 (55.2)	37 (55.2)	
Minor	30 (44.8)	30 (44.8)	
Previous upper abdominal surgery, *n* (%)	4 (6.0)	7 (10.4)	0.345[c]
Tumor size (cm), mean (SD)	5.04 ± 2.68	5.17 ± 2.22	0.755[a]
Number of tumors, *n* (%)			0.804[c]
Solitary	57 (85.1)	58 (86.6)	
Multiple	10 (14.9)	9 (13.4)	

AFP alpha-feto-protein, *ALB* albumin, *ALT* alanine transaminase, *ASA* American Society of Anesthesiologists, *AST* aspartate transaminase, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *F* female, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HTN* hypertension, *ICG* indocyanine green, *M* male, *SD* standard deviation, *TB* total bilirubin

[a]Student's test

[b]Fisher exact test

[c]Pearson χ^2 test

group than those in OGAH group. However, the overall morbidity rates of Clavien-Dindo grade III and above were similar (3.0% in the LGAH group and 10.4% in the OGAH group; $P=0.165$). Nevertheless, the length of postoperative hospital stay was shorter following LGAH than after OGAH (8.6 ± 5.4 vs. 10.6 ± 4.3 days, respectively; $P=0.024$).

Pathological characteristics

Pathological findings in the two groups are shown in Table 4. The variables of tumor number, tumor size, surgical margin, R0 resection, and histological liver cirrhosis were comparable in the two groups. The proportion of patients with satellite nodule and microvascular invasion were not significantly

Table 3 Surgical characteristics and surgical outcomes after propensity score matching

	Laparoscopic group ($n=67$)	Open group ($n=67$)	P value
Blood loss, mL (SD)	351.2 ± 328.4	357.5 ± 307.2	0.909[a]
Blood transfusion, *n* (%)	3 (4.5)	8 (11.9)	0.116[b]
Operation time, minutes (SD)	255.8 ± 100.4	201.5 ± 37.9	0.000[a]
Pringle maneuver, *n* (%)	51 (76.1)	45 (67.2)	0.250[b]
Clamping times, minutes (SD)	50.3 ± 23.8	35.5 ± 19.3	0.001[a]
Conversion to open laparotomy, *n* (%)	2 (2.9)	–	–
Type of resection, *n* (%)			0.747[c]
Right hepatectomy	25 (37.3)	22 (32.8)	
Left hepatectomy	9 (13.4)	12 (17.9)	
Left lateral sectionectomy	19 (28.4)	13 (19.4)	
Right posterior sectionectomy	9 (13.4)	12 (17.9)	
Right anterior sectionectomy	2 (3.0)	5 (7.5)	
Central hepatectomy(segments 4, 5, and 8)	2 (3.0)	2 (3.0)	
Extended left hepatectomy	1 (1.5)	1 (1.5)	
Postoperative hospital stay, days (SD)	8.6 ± 5.4	10.6 ± 4.3	0.024[a]
Mortality, *n* (%)	0 (0.0)	1 (1.5)	1.000[c]
Overall complications, *n* (%)	9 (13.4)	20 (29.9)	0.021[b]
Clavien-Dindo grade, *n* (%)			
I	4 (6.0)	7 (10.4)	0.345[b]
II	3 (4.5)	6 (9.0)	0.492[c]
III	1 (1.5)	4 (6.0)	0.365[c]
IV	1 (1.5)	2 (3.0)	1.000[c]
V	0 (0.0)	1 (1.5)	1.000[c]
Type of complication	($n=12$)	($n=25$)	
Pneumonia	2	4	
Pleural effusion	3	5	
Pulmonary embolism	0	1	
Ileus	1	1	
Peptic ulcer	0	1	
Wound infection	0	1	
Biliary leakage	1	2	
Ascites	3	6	
Intra-abdomen bleeding	1	2	
Liver failure	1	2	
Clavien-Dindo grade III and above, *n* (%)	2 (3.0)	7 (10.4)	0.165[c]
Comprehensive complication index	2.63 (0–43.3)	7.40 (0–100.0)	0.035[d]

SD standard deviation

[a]Student's test

[b]Pearson χ^2 test

[c]Fisher exact test

[d]Wilcoxon rank sum test

different. Moreover, the distribution of Edmonson-Steiner grade was also similar.

Oncological outcomes

HCC patients were followed to January 2018 and the survival time was calculated from the date of tumor resection to the date of death/recurrence or to the last follow-up. The median follow-up time were 19.5 months in LGAH group and 21 months in OGAH group, respectively. During the entire follow-up, tumour recurrence was observed in 16 of 67 patients (23.9%) after LGAH and in 13 of 67 patients (19.4%) after OGAH. The incidence of intrahepatic recurrence [13 (19.4%) for LGAH vs. 11 (16.4%) for OGAH,

Table 4 Pathological characteristics after propensity score matching

Pathological finding	laparoscopic group ($n=67$)	Open group ($n=67$)	P value
Histological cirrhosis, *n* (%)			0.471[b]
F4-cirrhosis	45 (67.2)	41 (61.2)	
Noncirrhotic[e]	22 (32.8)	26 (38.8)	
Microscopically R0 resection, *n* (%)			1.000[c]
Yes	66 (98.5)	65 (97.0)	
No	1 (1.5)	2 (3.0)	
Surgical margin (mm), mean(range)	13.40 (0–30.0)	15.7 (0–40.0)	0.065[d]
Tumor size, cm (SD)	5.04 ± 2.68	5.17 ± 2.22	0.755[a]
Satellite nodule, *n* (%)			0.069[b]
Yes	9 (13.4)	3 (4.5)	
No	58 (86.6)	64 (95.5)	
Microvascular invasion, *n* (%)			0.458[b]
Yes	11 (16.4)	8 (11.9)	
No	56 (83.6)	59 (88.1)	
Edmonson-Steiner grade, *n* (%)			0.717[c]
I	4 (6.0)	7 (10.4)	
II	38 (56.7)	34 (50.7)	
III	24 (35.8)	24 (35.8)	
IV	1 (1.5)	2 (3.0)	

SD standard deviation

[a]Student's test

[b]Pearson χ^2 test

[c]Fisher exact test

[d]Wilcoxon rank sum test

[e]Including chronic hepatitis and normal liver tissue

respectively; $P=0.652$] and extrahepatic recurrence [3 (4.5%) for LGAH vs. 2 (3.0%) for OGAH, respectively; $P=1.000$] were also similar in both groups. Treatment of intrahepatic recurrences in the LGAH group was repeat open hepatectomy in three, salvage liver transplantation in one, radiofrequency ablation (RFA) in two, transcatheter arterial chemoembolization (TACE) in five, palliative treatment in two patients. In the OGAH group, repeat open hepatectomy was performed in three patients, RFA in three, TACE in four, and one patient had palliative treatment. In addition, no

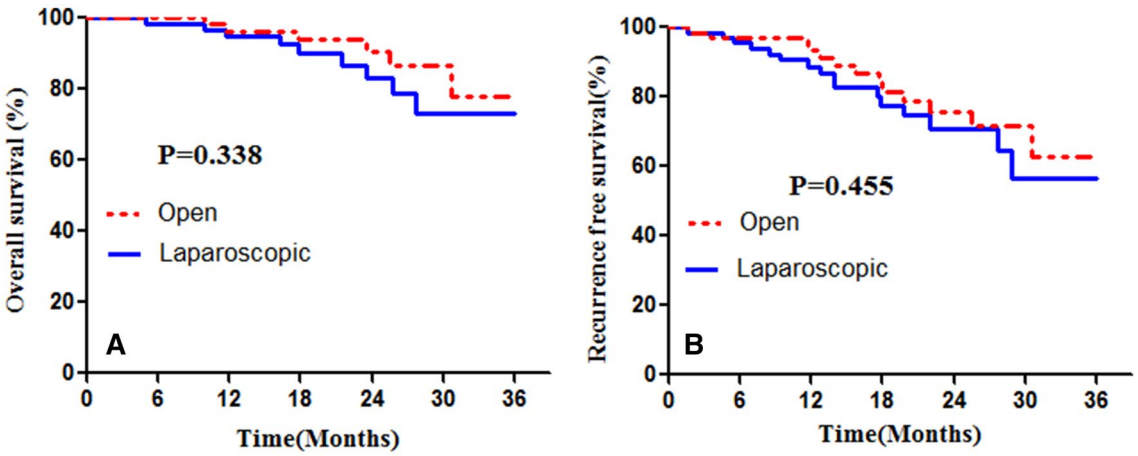

Fig. 2 The survival curve between the laparoscopic and open Glissonian pedicle approach hepatectomy groups. **A** Overall survival rates. **B** Recurrence-free survival rates

patient in the LGAH group experienced port site recurrence or peritoneal implantation.

The 1-, and 3-year overall survival rates were 94.9%, and 73.3%, in the LGAH group, and 96.4%, and 77.8% in the OGAH group, respectively (Fig. 2A). The 1-, and 3-year disease-free survival rates were 88.7%, and 56.4% in the LAH group and 93.2%, and 62.5% in the OAH group, respectively (Fig. 2B). There were no significant differences between the groups regarding the 1, 3-year overall survival rate ($P = 0.338$) or the 1, 3-year disease-free survival rate ($P = 0.455$).

Discussion

The Glissonian pedicle approach is a technical procedure widely used among open hepatectomies which have several advantages over standard liver resection including shorter operative time, lower intraoperative hemorrhage, and morbidity [15–17, 34]. Meanwhile, a previous study had also demonstrated the benefits of Glissonean approach in patients with HCC [18]. With the advancement of laparoscopic techniques and surgical equipment, the Glissonian approach has been increasingly proposed as a safe and efficient method for laparoscopic liver surgery [19–21]. In recent, Machado et al. [10] performed the first comparison between the Glissonian and the standard approach in laparoscopic liver resection and found that intrahepatic Glissonian approach had several advantages over standard LH. However, no systematic study has directly compared the perioperative and oncological outcomes of LGAH with OGAH for HCC. To the best of our knowledge, this is the first study investigating the perioperative and oncological outcomes of LGAH versus OGAH for HCC patients. Firstly, we found that both the LGAH and OGAH were safe and efficient for HCC patients, even in some patients with cirrhosis. Secondly, the LGAH was associated with lower overall complication rates and lower CCI when compared with the OGAH. Furthermore, we found that both the 3-year overall survival rate and 3-year disease-free survival rate were comparable between the groups.

The recent Morioka Consensus Conference of laparoscopic liver surgery stated: "In the case of right or left hepatectomy, the Glissonian approach serves as an important alternative to hilar dissection approach and only surgeons experienced with this technique should use it" [35]. It suggests that the laparoscopic Glissonian pedicle approach liver resection was not widely accepted as in open hepatectomy and associated with some technical challenges. One of the most important technical challenges was difficulty in encircling the Glissonian pedicles laparoscopically because of movement limitations of the instruments during laparoscopic procedures [36]. When encircling the Glissonian pedicles laparoscopically, impertinent and forceful maneuvers can sometimes result in excessive bleeding and bile duct injury. Hence, Cho et al. [21] proposed the method of a extrahepatic Glissonian approach using special instruments to encircle the Glisson pedicle and concluded that it is a feasible method. Meanwhile, Machado et al. [19] proposed another method of an intrahepatic Glissonian approach by adding two small incisions on both sides of the Glissonian pedicle in which to insert the stapler. In recent, Lee et al. [24] reported that the pedicle can be easily encircled after sufficient parenchymal dissection is done so that the whole Glissonian pedicle structures are visualized. In the present study, we had routinely encircled the corresponding Glissonean pedicle by the method of Cho et al. [21]. In case of difficulty in encircling the pedicles before parenchymal dissection, the corresponding Glissonean pedicle could be encircled after sufficient parenchymal dissection was finished. In this study, we did not encounter the technical failure of the laparoscopic Glissonian pedicle approach which was caused by difficulty in encircling the pedicles. Finally, we thought that the method of Lee et al. [24] was the simplest way for encircling the Glissonian pedicles, especially for the inexperienced surgeons.

The fear of an inadvertent pedicle injury during the use of linear stapler may be another technical challenge. In our institution, the following strategies were used to address this issue. Firstly, preoperative three-dimensional reconstruction CT/MRI were performed to identify potential anatomic variations of the portal triad, especially the aberrant bile duct anatomy, when considering the Glissonian pedicle approach. If the variations were found by the preoperative assessment of imaging examinations, the Glissonean pedicle approach will not be chosen. Secondly, the intraoperative ultrasonography could routinely be used to ascertain the localization of the pedicles if necessary. Last but not least, we did not transect the Glissonean pedicle before the sufficient parenchyma dissection is done as described by Lee et al. [24]. When the whole bifurcating Glissonian pedicle was exposed, we transected the hepatic pedicle tissue by the laparoscopic linear stapler. During stapling was done, the first assistant retracted the tape toward the contralateral side which could prevent injury or stricture of the contralateral Glissonian pedicle branch. In our institution, we had no case with such a bile duct injury when using the laparoscopic Glissonian pedicle approach. Of course, every novel approach will result in a learning curve and may require proctoring by experienced surgeons, when the Glissonian pedicle approach is first used.

Consistent with some previous PSM studies [37, 38] which investigated outcomes of laparoscopic versus open liver resection for HCC, we found that the overall rate of postoperative complications were significantly lower in patients who underwent LGAH than OGAH for HCC. This study shows that the most common complications for the both groups were similar, including ascites, pleural effusion

and pneumonia. Laparoscopic operations have the advantages of preservation of the abdominal wall collaterals and less manipulation, which may lead to decrease the incidence of postoperative ascites [39]. Moreover, the laparoscopic approach has been shown to reduce wound size and cause less pain, which allows patients to resume walking activity and breathing exercises earlier after surgery, thereby theoretically causing fewer pulmonary complications [40]. In the current study, the incidence of ascites (3/67 vs. 6/67) and pulmonary complications(5/67 vs. 10/67) were lower in LGAH group than that in OGAH group, although each complication rate did not reach a significant statistical difference. Nevertheless, the overall rate of complications and Clavien-Dindo grade for complication could not be used to accurately evaluate the severity of complication for a single patient who can suffer from several complications. In order to evaluate the complications accurately, we choose to use the recently upgraded scoring system, the CCI, as a safety outcome, because it assesses all complications, not just the most severe, and allows the expression of complications on a scale of 1–100 [28]. Similarly, we found that LGAH was associated with significantly lower CCI, which suggested a lower severity of postoperative complications after LGAH.

In addition, the present study suggested that operative time in the LGAH group was significantly longer than that of OGAH group. The relatively longer operative duration could be attributed to the wide application of Pringle maneuver during parenchyma transection. As described by Yoon et al. [41], much of the operative time was spent cutting the liver parenchyma, which had an impact on the Pringle maneuver clamping time. In the current study, the need of Pringle maneuver in the LGAH group was more common than that of OGAH, although it did not reach a significant statistical difference. However, the overall Pringle clamping time in LGAH group was significantly longer than OGAH group(50.3 ± 23.8 vs. 35.5 ± 19.3, respectively, $P = 0.001$). What's more, the potential effect of learning curve may be another explanation for the relatively longer operative duration. Although we have passed the basic learning curve of LGAH during the research period (2015–2017), the level of skills in LGAH was less than those of more than one thousand OGAH experience in our center. Interestingly, this study failed to demonstrate a reduction in blood loss in the LGAH group, which was consistent with the findings in a multicentric PSM study from Japan of laparoscopic liver resection in patients with HCC [37].

With respect to the oncological outcomes, we found that both the 3-year overall survival rate and disease-free survival rate were comparable between the two groups. As is known to all, both the impertinent manipulation during hepatectomy (such as positive surgical margin) and the biological behavior of the HCC will influence the prognosis of HCC patients. In our institution, the standard for laparoscopic Glissonian approach liver resection was very strict, which required that the laparoscopic hepatectomy must be performed in the same manner as open hepatectomy. For example, the major hepatic vein (MHV) should be exposed on the cutting plane for anatomical hepatectomy via a pure laparoscopic approach (Fig. 3). Nevertheless, some surgeons may have a concern that LGAH would decrease the tumor-free surgical margin because of the lack of palpation. However, instead of palpation, intraoperative ultrasound and the intrahepatic landmarks (such as MHV) can be used to help laparoscopic surgeons to obtain adequate tumor-free margins for hepatectomy. Recently, we have gradually introduced ICG fluorescence imaging in HCC patients during laparoscopic liver resection according to the guidance of literature [42], which can guide laparoscopic surgeons to confirm the locations of tumor at any time. In the present study, tumor-free surgical margin was similar in both groups. Moreover, the pathological findings suggest the biological behaviors of the HCC were also comparable in the two groups. Therefore, the standardization of operation and the similar characteristics of tumor are expected to contribute to the equivalence of oncologic outcomes between the two groups.

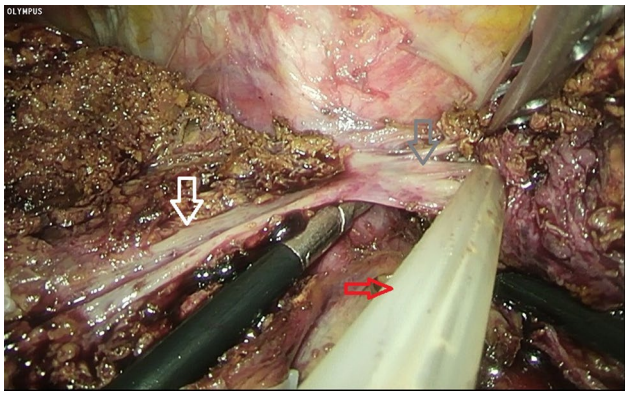

Fig. 3 The middle hepatic vein was exposed on the cutting plane in a case of laparoscopic left hemihepatectomy. white arrow, middle hepatic vein; gray arrow, the root of left hepatic vein; red arrow, laparoscopic CUSA. (Color figure online)

In this study, several limitations need to be addressed. Firstly, the potential effects of a learning curve in the laparoscopic approach may exist objectively. The first case of LGAH in our center was a left lateral lobectomy performed in 2009 and more than 40 cases of LH were performed until 2015 [43]. The first case of laparoscopic Glissonian approach right hemihepatectomy was successfully operated in 2015. Therefore, we included patients who underwent LGAH only after 2015 to limit the influence of learning curve as less as possible. However, the level of skills in LGAH was less than that of more than one thousand OGAH experience in our center. Moreover, the operative time of laparoscopic Glissonian approach right hemihepatectomy

in the recent patients was reduced by about two hours compared with the time required for the first 5 patients. The improved results may well be related to a learning curve in the laparoscopic Glissonian pedicle approach. Secondly, the current study was conducted using retrospective analysis of a single-center prospective database. To overcome selection bias as far as possible, a propensity score matching was employed because this model was deemed as the most effective method to balance the covariates and thus reducing bias in the retrospective studies. Last but not least, our results should be interpreted with caution because our cohort was composed of patients without anatomic variations of the portal triad. As reported by literature, the presence of anatomic variations was common reasons for technical failure and unfeasibility of the Glissonian approach [44]. Therefore, when considering the Glissonian approach, the presence of anatomic variations of the portal triad should always be considered.

In conclusion, this study assesses the feasibility and outcomes of pure LGAH for HCC by comparing with OGAH. The current study found that pure LGAH for HCC could be feasibly and safely performed in selected HCC patients, which may be associated with fewer complications, shorter postoperative hospital stay and comparable oncological outcome compared to OGAH. These results suggest that pure laparoscopic Glissonian approach may be a better alternative to open Glissonian approach in selected HCC patients.

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Compliance with ethical standards

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