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Cutting-edge liver surgery-based modalities for diagnosis and treatment of liver tumors

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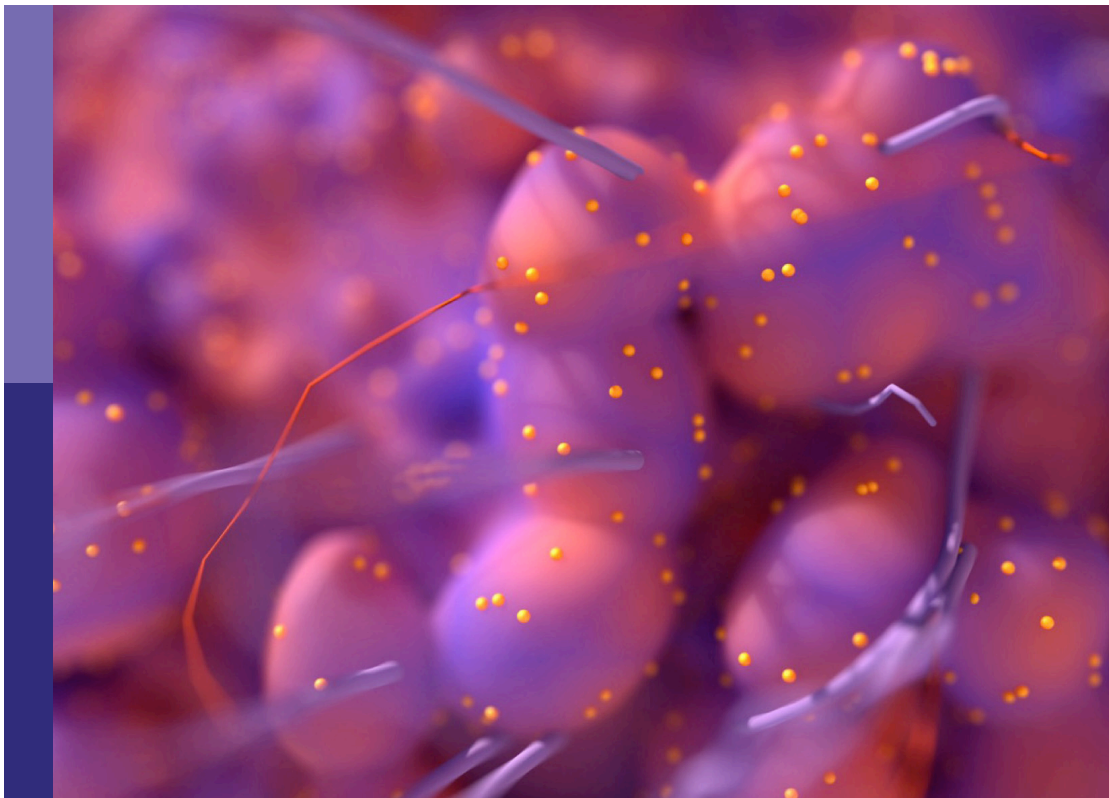

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Cutting-edge liver surgery-based modalities for diagnosis and treatment of liver tumors

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Editorial: Cutting-edge liver surgery-based modalities for diagnosis and treatment of liver tumors

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liver surgery, laparoscopic liver resection, prognosis prediction, complication treatment, perioperative management

Editorial on the Research Topic
Cutting-edge liver surgery-based modalities for diagnosis and treatment of liver tumors

Liver cancer is a common type of malignant tumor in digestive system with high morbidity and mortality worldwide. While surgical resection remains the principal treatment choice, accurate preoperative evaluation, individualized surgical planning, standardized surgical procedures, and appropriate perioperative management are crucial for the prognosis of liver cancer after surgery. This Research Topic embodies 9 multidisciplinary manuscripts focused on multifaceted aspects related to "*Cutting-edge liver surgery-based modalities for diagnosis and treatment of liver tumors*."

With the development of laparoscopic technique and equipment, laparoscopic liver resection (LLR) has been widely applied at present. To further determine the long-term outcome of LLR for hepatocellular carcinoma (HCCs), Tian et al.'s group conducted a retrospective study with 1773 HCC patients included and found that LLR for HCCs showed better short-term outcomes and comparable long-term outcomes with laparoscopic liver resection (OLR). Moreover, Xi et al. developed a novel difficulty scoring system to predict the surgical difficulty of LLR, which can help the surgeons to improve the surgical plan and safety. It will become a future trend that using laparoscopic technique in the treatment of different liver tumors.

Both proper hepatic inflow occlusion and hepatic venous system hemorrhage control are essential for the safety of liver resection. Qu et al.'s group retrospectively analyzed and shared their experience of dealing with Intraoperative hepatic venous system hemorrhage and carbon dioxide gas embolism during LLR. Shi et al. found that while regional and intermittent hepatic inflow occlusion are equally safe and effective, the former showed more advantageous in operation continuity, intraoperative bleeding, and postoperative

liver function recovery in LLR. Zhao et al.'s group introduced the technique of counterclockwise modular laparoscopic anatomic mesohepatectomy using combined Glissonean pedicle and hepatic vein-guided approaches. Besides low central venous pressure technique, Wang X. et al. reported that application of dexmedetomidine during anesthesia improved liver function post hepatectomy. As technology advances, injuries during liver surgery will be better controlled and more patients could be benefited.

In addition to these technical improvements, prognostic factors of liver cancers were also analyzed. Wang, Q. et al. conducted a systematic review and reported that sarcopenia prevalent in patients undergoing PVE/ALPPS might be a risk factor for impaired liver growth. Ge et al. found that both the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio could be used to effectively predict long-term survival in patients with perihilar cholangiocarcinoma who underwent curative resection. Sun et al.'s group identified adjuvant TACE timing after radical resection as an independent prognostic factor for patients with HCCs. Effective prognostic prediction is also helpful for the formulation of clinical intervention strategies.

Altogether, the original articles and reviews collected in this Research Topic provide new insights on important achievements obtained in therapeutic strategies, surgical procedure, perioperative management, and analysis of prognostic factors of liver cancers.

Author contributions

HH: Writing – review & editing, Investigation. YG: Writing – review & editing. XZ: Writing – review & editing. YZ: Writing – review & editing. HZ: Writing – original draft, Writing – review & editing, Supervision

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A novel difficulty scoring system of laparoscopic liver resection for liver tumor

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Objectives: To develop a novel difficulty scoring system (NDSS) to predict the surgical difficulty of laparoscopic hepatectomy.

Patients and methods: A total of 138 patients with liver tumors performed liver resection (LLR) between March 2017 to June 2022 were selected from Affiliated Hospital of Jiangnan University and Wujin Hospital Affiliated with Jiangsu University.Patient demographics, laboratory tests, intraoperative variables, pathological characteristics were assessed. We also assessed the Child Pugh score and the DSS-B score.

Results: Patients were divided into training and testing cohort according to their hospital. Patients in training cohort were divided into high and low difficult groups based on operation time, blood loss and conversion. Higher percentage of patients with malignant liver tumor (87.0% vs. 58.1%; $P = 0.003$) or history of hepatobiliary surgery (24.1% vs. 7.0%; $P = 0.043$) in high difficult group than in low difficult group. To improve the difficulty scoring system, we incorporated the history of hepatobiliary surgery and nature of the tumor. A novel difficulty scoring system was established. The results showed that the operation time ($P < 0.001$), blood loss ($P < 0.001$), ALT ($P < 0.001$) and AST ($P = 0.001$) were associated with the novel difficulty score significantly. Compared with DSS-B, the NDSS has a higher area under the receiver operating characteristic (AUROC) (0.838 vs. 0.814). The nomogram was established according to the NDSS. The AUROCs of the nomogram in training and testing cohort were 0.833 and 0.767. The calibration curves for the probability of adverse event showed

optimal agreement between the probability as predicted by the nomogram and the actual probability.

Conclusions: We developed a nomogram with the NDSS that can predict the difficulty of LLR. This system could more accurately reflect the difficulty of surgery and help liver surgeons to make the surgical plan and ensure the safety of the operation.

KEYWORDS

difficulty scoring system, laparoscopic surgery, liver resection, liver tumor, outcome

Introduction

With the first case of laparoscopic liver resection (LLR) reported in 1992, LLR as a treatment for liver tumors has been developed in major centres (1, 2). In the early days after LLR was introduced, it was limited to local hepatectomy, but now expanded hemihepatectomy and laparoscopic repeat liver resection (LRLR) are no longer contraindicated (3). Compared to open liver resection (OLR), there was less blood loss, shorter hospital stays, and fewer postoperative complications (4). In 2008, the first International Consensus Conference on Laparoscopic Hepatectomy (ICCLLR) was held in the United States, where LLR was identified as a safe and effective treatment for liver disease (5). And in 2014, the second ICCLLR was held in Japan, where the surgical indications were expanded and highlighted the assessment of surgical difficulty was believed important (6). The most used difficulty scoring system was Ban Difficulty Scoring System (DSS-B), which was developed by Japanese scientists Ban in 2014 (7). The scoring system included five factors: the extent of liver resection, tumor location, tumor size, proximity to major blood vessels, and Child-Pugh score of liver function. With the development of LLR around the world in recent years, some other factors affecting the difficulty of LLR have been gradually found. For instance, Uchida et al. assessed the surgical outcomes of LLR in patients with liver cirrhosis with specific reference to a difficulty scoring system (8). Kinoshita et al. investigate the predictive factors and classifications for the difficulty of laparoscopic repeated liver resection (LRLR) in patients with recurrent hepatocellular carcinoma (9). In addition, Takase et al. found that the operation time of LRLR was longer than that of laparoscopic primary liver resection (LPLR). Moreover, there was no score for caudate lobe tumors in DSS-B. Based on the above, we believed that some other factors including the history of hepatectomy may also increase the difficulty of LLR. Therefore, we intend to develop a novel difficulty scoring system (NDSS) to predict the surgical difficulty of laparoscopic hepatectomy.

Methods

Patients

From December 2020 to March 2022, 97 patients (training cohort) who performed LLR for liver tumor were selected at the Department of Hepatological Surgery, Affiliated Hospital of Jiangnan University. From March 2017 to June 2022, 41 patients (testing cohort) who performed LLR for liver tumor were selected at the Department of General Surgery, Wujin Hospital Affiliated with Jiangsu University. Patients who had also undergone lymph node dissection or other organ resection (except cholecystectomy) were excluded. This research was approved by the Ethics Committee of the Affiliated Hospital of Jiangnan University (LS2021078) and Wujin Hospital Affiliated with Jiangsu University (2022-SR-084).

Data collection

Patient demographics included age, gender, comorbidity, and history of surgery. Laboratory tests included alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), prothrombin time (PT), total bilirubin (TB), white blood cell count (WBC), C-reactive protein (CRP). Intraoperative variables included operation time, blood loss, blood transfusion and postoperative stay (POS). Pathological characteristics included tumor size, tumor position, and pathological pattern. We also assessed the Child-Pugh score and the DSS-B score (7, 10). To accommodate all patients, we rated caudate lobe tumors at 5 points. The detailed grading is shown in Figure 1. Postoperative complications included haemorrhage, bile leakage, ileus, pneumonia, pleural effusion, abdominal infection, liver failure, and incision infection. Postoperative hospitalization days were also recorded.

Difficulty of laparoscopic liver resection												
12-level Index	1	2	3	4	5	6	7	8	9	10	11	12
Three-level index	Low					Intermediate			High			

Location of tumor		Liver function		Size of tumor	
S1	5	Child–Pugh A	0	<3 cm	0
S2	2	Child–Pugh B	1	≥3 cm	1
S3	1				
S4	3	Proximity to major vessel		Type of resection	
S5	3	No	0	Partial resection	0
S6	2	Yes	1	Left lateral sectionectomy	2
S7	5			Segmentectomy	3
S8	5			Not less than a sectionectomy	4

FIGURE 1
Indexes of difficulty of laparoscopic liver resection based on LLR-B.

Statistical analysis

Statistical analyses were conducted with Prism 9.0.1 (GraphPad Software, LLC). For continuous variables, data were expressed as mean ± standard deviation (SD), and the differences between the two groups were analyzed by the two independent samples Student t-test and Mann Whitney test. The differences among groups (more than two) were analyzed by one-factor analysis of variance (One-Way ANOVA). For categorical variables, the differences between groups were analyzed by the chi-square test, Chi-square with Yates' correction, and Fisher's exact test according to the sample size. Linear regression was used to predict the correlation between variables. The accuracy of different difficulty scoring systems was compared by the receiver operating characteristic (ROC) curve. Calibration plot for incidence of high difficulty was generated to assess the performance characteristics of the constructed difficulty scoring systems. The nomograms were established by the "rms" package in R version 4.2.0. We also draw the calibration plots for the adverse event rate were generated to assess the performance characteristics of the constructed nomograms. Bootstraps with 1000 resample were used for validation of the nomogram and C-index. The ROC curve and calibration plot were drawn by RStudio software (Version 1.4.1103).

Results

Patient characteristics and surgical outcomes

The flow chart of the study is shown in Figure 2. Among the 97 patients in training cohort, 40 (41.2%) patients had a history of abdominal surgery and 16 (16.5%) patients had a history of hepatobiliary surgery in them. Based on the preoperative history of hepatobiliary surgery, we classified patients into two groups: laparoscopic liver resection after previous hepatobiliary surgery (LLRAH) and laparoscopic liver resection with no hepatobiliary surgery (LLRNH). The characteristics and surgical outcomes of LLR between LLRAH and LLRNH groups were shown in Table 1. The results showed that patients in the LLRAH group were older and had more comorbidities compared to those in the LLRNH group (65.1 ± 8.6 vs. 56.2 ± 12.7; $P = 0.009$). And the operation time of LLR for patients in the LLRAH group was longer than that in the LLRNH group. Therefore, we believed that the history of hepatobiliary surgery was one of the important factors affecting the difficulty of LLR.

Establish and validate a novel difficulty rating system

It is well known that the operation time, blood loss and conversion to open surgery reflect surgical difficulty. An adverse event was defined when the operation time exceeded 240 minutes or the blood loss exceeded 400 ml, or when the operation was switched to open surgery. Therefore, we believed that the operation was difficult when adverse event occurred. Based on this, patients were divided into high and low difficult group. The characteristics and surgical outcomes of LLR between high difficult and low difficult groups were shown in Table 2. The results showed that patients in high difficult group were older (60.1 ± 11.4 vs. 54.5 ± 13.3; $P = 0.030$) and had higher difficult score (DSS-B, high difficult, 51.9% vs. 7.0%, $P < 0.001$) compared to those in low difficult group. And higher percentage of patients with malignant liver tumor (87.0% vs. 58.1%; P =

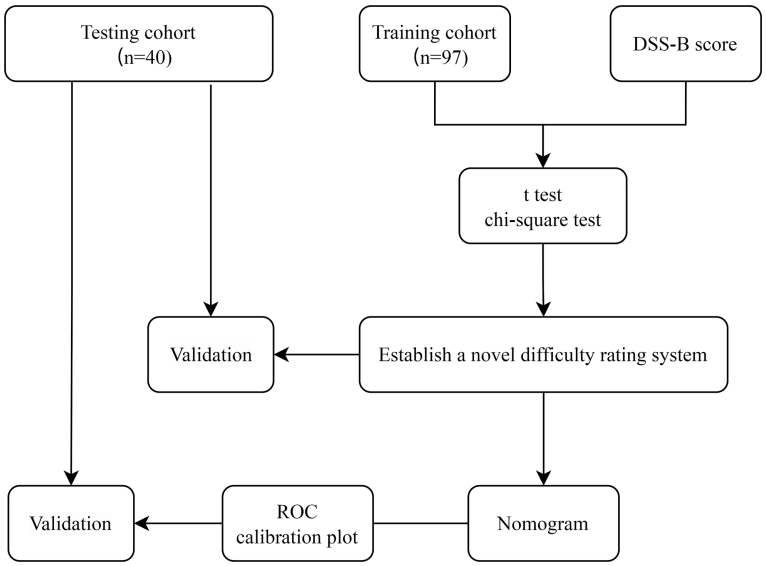

FIGURE 2
The flowchart of our research. ROC, receiver operating characteristic.

0.003) or history of hepatobiliary surgery (24.1% vs. 7.0%; P = 0.043) in high difficult group than in low difficult group. To improve the difficulty scoring system, we incorporated the history of hepatobiliary surgery and the nature of the tumor. A novel difficulty scoring system was established as shown in Figure 3. A history of hepatobiliary surgery or malignancy was each assigned a score of 1. The NDSS for a liver tumor in this study ranged from 1 to 13 (Table 3; Figure 4). The results showed that the operation time (P < 0.001), blood loss (P < 0.001), transfusion (P < 0.001), ALT (P < 0.001) and AST (P = 0.001) were associated with the novel difficulty score significantly. The area under the receiver operating characteristic (AUROC) was used to verify the accuracy of the NDSS in predicting surgical difficulty of LLR for patients with a liver tumor. Compared with DSS-B, the NDSS has a higher AUROC (0.838 vs. 0.814, Figure 5A). The C-index of the DSS-B was 0.814 (95% CI: 0.731-0.897). The C-index of the NDSS was 0.838 (95% CI: 0.762-0.914). Additionally, the calibration plots of DSS-B and NDSS had a good coherence between the predictions and actual values in predicting surgical difficulty, as shown in Figures 5B, C.

Subgroup analysis

We compared the intraoperative outcomes among cases classified as low (NDSS 1-5), intermediate (NDSS 6-9), high (NDSS 10-14) difficulty. The results showed that the operation time (P < 0.001), blood loss (P = 0.001), transfusion (P = 0.008), POS (P = 0.041), ALT (P = 0.002) and AST (P = 0.006) were significantly different among these subgroups (Table 4). And its correlation was shown in Figure 6.

Development and validation the nomogram of adverse event

The NDSS were incorporated into the nomograms (Figure 7A). In the training cohort, the AUROC of the nomograms was 0.833 (Figure 7B). To validate the nomogram, 41 patients (testing cohort) who performed LLR were selected from Wujin Hospital Affiliated with Jiangsu University. The characteristics between training and testing cohort were shown in Table 5. In the testing cohort, the AUROC of the nomogram for predicting the adverse event (the degree of surgical difficulty) was 0.767 (Figure 7C). The calibration plots of the nomogram had a good coherence between the predictions and actual values in the probability of adverse event in both training and testing cohorts, as shown in Figures 7D–E.

Discussion

LLR has rapidly become widespread all over the world (11). In recent years, more and more surgical centres have included laparoscopic hepatectomy in the routine treatment of liver tumors, and the proportion is gradually increasing, and is up to 30.8% of liver resection (LR) (3). At the European Guidelines Meeting for Laparoscopic Liver Surgery, it was noted that LLR was a complex surgical skill that must be mastered in a progressive manner (12). The conventional advice is to start with a small or left lateral lobectomy and then perform a major resection as the experience increases. In addition, this simplification overlooked factors that affect laparoscopic liver

TABLE 1 Patient characteristics and surgical outcomes of LLR between LLRAH and LLRNH.

Characteristic	LLRAH (16)	LLRNH (81)	*P* value
Age, years	65.1 ± 8.6	56.2 ± 12.7	0.009*
Gender, male/female	11/5	50/31	0.595
Hypertension, yes/no	10/6	21/60	0.004*
Diabetes, yes/no	7/9	10/71	0.003*
POS, days	10.6 ± 4.0	11.3 ± 6.8	0.722#
Child-Pugh, A/B	15/1	80/1	0.743$
Tumor size, mm	38.5 ± 29.9	49.1 ± 29.5	0.195
DSS-B, L/I/H[a]	3/6/7	23/34/24	0.256
Pringle, yes/no	13/3	69/12	0.984$
Operation time, min	291.6 ± 90.9	221.3 ± 99.8	0.011*
Bleeding, ml	343.8 ± 392.0	258.2 ± 307.6	0.508
Transfusion, yes/no	2/14	11/70	0.775$
Conversion, yes/no	1/15	7/74	0.858$
Malignant, yes/no	15/1	57/24	0.101$
Postoperative morbidity	3/13	13/68	0.918$
Hemorrhage, yes/no	0/16	1/80	n.s†
Bile leakage, yes/no	0/16	4/77	n.s†
Ileus, yes/no	0/16	1/80	n.s†
Pneumonia, yes/no	1/15	2/79	0.994$
Pleural effusion, yes/no	1/15	2/79	0.994$
Abdominal infection, yes/no	1/15	1/80	0.743$
Liver failure, yes/no	0/16	1/80	n.s†
Incision infection, yes/no	0/16	2/80	n.s†
Postoperative day 1 (POD1)			
ALT, U/L	249.6 ± 209.4	445.8 ± 501.0	0.170#
AST, U/L	263.3 + 186.8	401.4 + 390.2	0.363#
TB, umol/L	19.1 ± 9.3	22.0 ± 14.1	0.431
WBC, *10^9/L	11.5 ± 4.3	12.3 ± 4.2	0.487
CRP, mg/L	44.1 ± 36.2	42.6 ± 40.5	0.889

LLR, laparoscopic liver resection; LLRAH, laparoscopic liver resection after previous hepatobiliary surgery; LLRNH, laparoscopic liver resection with no hepatobiliary surgery; POS, postoperative stay; DSS-B, Ban Difficulty Scoring System; n.s, not significant; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; WBC, white blood cell count; CRP, C-reactive protein.
*Statistically significant; #Mann-Whitney test; $Chi-square with Yates' correction, †Fisher's exact test.
[a]L, low (1–5); I, intermediate (6–8); H, high (9–12).

resection difficulties difficulty, such as the relationship between neoplasms and large vessels and the history of liver resection. Hence a simple, objective, and robust preoperative difficulty scoring system could help surgeons master the procedure step by step.

For the past few years, a difficulty grading system of LLR has been proposed by experts (7, 13–17). Ban et al. analyzed clinical data and difficulty index of 30 patients, screened out 5 independent risk factors affecting LLR difficulty, and established the DSS-B using a linear regression model (7). The impact of different types of laparoscopic surgery was not considered in DSS-B, such as total laparoscopic hepatectomy, hand-assisted laparoscopic hepatectomy, on the difficulty of LLR, making the difficulty score incomplete. Therefore, some scholars improved DSS-B and launched an upgraded version of the IWATE Criteria for difficulty scoring (13). Different from DSS-B, Hasegawa et al. used operation time as the indicator of surgical difficulty, evaluated the influence of preoperative factors on operation time through multiple linear regression analysis, and included BMI as a difficulty scoring factor for the first time (14). In 2018, Kawaguchi et al. developed a difficulty scoring system based on the extent of resection (DSS-ER) (15). For the first time, operation time, blood loss and conversion rate were used as difficulty criteria, and the median was used as the cutoff value. However, this scoring system was based on the intraoperative results and ignored the preoperative and postoperative factors, and the verification was carried out by postoperative results, which might have a certain bias. In addition, it only considered the type of resection and ignored the influence of factors such as the general state of the patients and tumors on the operation, so its accuracy might be affected. In the same year, Halls et al. reported on a difficulty scoring

TABLE 2 Patient characteristics and surgical results of laparoscopic liver resection.

Characteristic	High difficult (54)	Low difficult (43)	*P* value
Age, years	60.1 ± 11.4	54.5 ± 13.3	0.030*
Gender, male/female	37/17	24/19	0.198
Hypertension, yes/no	21/33	10/33	0.101
Diabetes, yes/no	11/43	6/37	0.409
HOA, yes/no	26/28	14/29	0.121
HOH, yes/no	13/41	3/40	0.048*
HOL, yes/no	7/47	0/43	0.016†*
Child-Pugh, A/B	53/1	42/1	0.578$
Malignant, yes/no	47/7	25/18	0.003*
Tumor size, mm	51.2 ± 32.5	42.5 ± 25.3	0.152
DSS-B, L/I/H[a]	5/21/28	21/19/3	<0.001*
Pringle, yes/no	49/5	33/10	0.058
Operation time, min	297.1 ± 84.6	152.2 ± 49.7	<0.001#*
Bleeding, ml	440.7 ± 368.5	111.6 ± 55.5	<0.001#*
Transfusion, yes/no	13/41	0/43	<0.001†*
Conversion, yes/no	8/46	0/43	0.008†*
POS, days	12.7 ± 6.9	10.0 ± 5.9	0.018*
Postoperative morbidity, yes/no	11/43	5/38	0.249
Hemorrhage, yes/no	0/53	1/43	n.s†
Bile leakage, yes/no	4/50	0/43	0.127†
Ileus, yes/no	1/53	0/43	n.s†
Pneumonia, yes/no	2/52	1/42	0.841$
Pleural effusion, yes/no	3/51	0/43	0.327†
Abdominal infection, yes/no	2/15	0/80	0.501†
Abdominal effusion, yes/no	1/53	1/42	0.578$
Liver failure, yes/no	1/53	0/43	n.s†
Incision infection, yes/no	0/52	2/43	0.194†
Postoperative day 1 (POD1)			
ALT, U/L	564.6 ± 553.5	223.7 ± 230.6	<0.001#*
AST, U/L	501.5 + 406.1	224.3 + 238.0	<0.001#*
TB, umol/L	22.5 ± 12.3	20.2 ± 14.6	0.417
WBC, *10^9/L	12.5 ± 4.6	11.7 ± 3.6	0.330
CRP, mg/L	41.2 ± 37.9	45.0 ± 42.0	0.646

HOA, history of abdominal surgery; HOE, history of epigastric surgery; HOH, history of hepatobiliary surgery; HOL, history of liver surgery; POS, postoperative stay; DSS-B, Ban Difficulty Scoring System. n.s, not significant; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; WBC, white blood cell count; CRP, C-reactive protein.
*Statistically significant; #Mann-Whitney test; $Chi-square with Yates' correction; †Fisher's exact test.
[a]L, low (1-5); I, intermediate (6-8); H, high (9-12).

system based on data from seven centres (16). For the first time, previous open liver surgery history and preoperative neoadjuvant chemotherapy were factored into the scoring system. However, the definition of preoperative neoadjuvant chemotherapy in this study was very vague, and there was a lack of data about the time and cycle of neoadjuvant chemotherapy, so the actual prediction results might be biased to some extent. Subsequently, Tong et al. proposed Sir Run Run Shaw Hospital (SRRSH) risk models based on conversion and complication. For the first time, this scoring system included the American society of anesthesiologists (ASA), ALT, cirrhosis and other indicators that reflect the general situation of patients and was a prediction model for the feasibility and safety of LLR. However, most of the cases in this study were small-scale hepatectomy, which might lead to selection bias. Therefore, more cases were needed to prove the application of SRRSH score in large-scale hepatectomy. The difficulty scoring system reported previously did not contain all the factors affecting surgery, which affects their accuracy. In addition to the above factors, Guilbaud et al. reported that an estimated parenchymal transection surface area ≥ 100 cm^2 was a relevant indicator of surgical difficulty and postoperative complications in LLR (18).

In the present study, the high difficulty outcome events were identified as blood loss > 400 ml, and operation time > 240 min

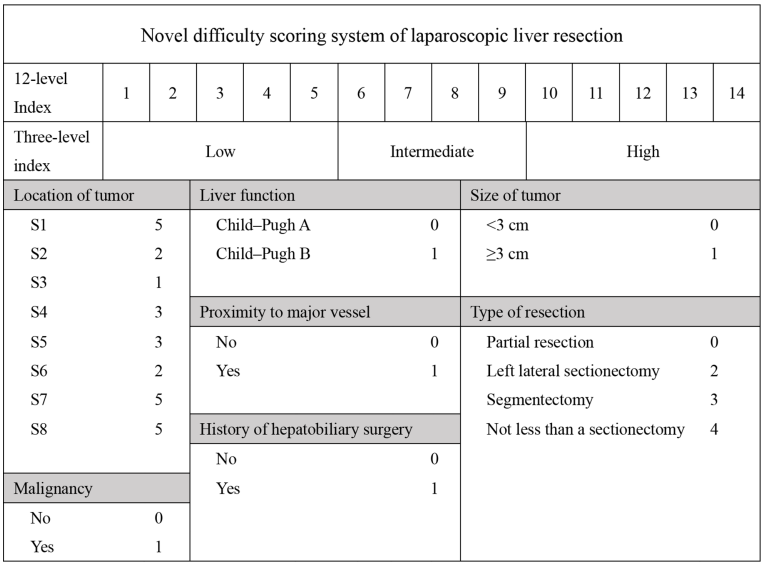

FIGURE 3
Indexes of the novel difficulty of laparoscopic liver resection.

or conversions. The measures of surgical difficulty were similar to DSS-ER (15). But the specific reference values were different. This difference may have to do with the different measures used by different centres. Through correlation analysis, age, history of hepatobiliary surgery (HOH), history of liver surgery (HOL), and malignant and DSS-B were closely related to surgical difficulty. Based on clinical experience and the results of other centres, age was not a direct factor affecting the difficulty of LLR.

TABLE 3 Surgical outcomes according to the novel difficulty rating system (n=97).

Score	1 (n=1)	2 (n=1)	3 (n=2)	4 (n=3)	5 (n=10)	6 (n=11)	7 (n=9)	8 (n=16)	9 (n=12)	10 (n=14)	11 (n=11)	12 (n=6)	13 (n=1)	*P* value
Operation time, min	55.0	90.0	45.0	95.0 ± 5.0	151.0 ± 21.7	176.8 ± 50.8	237.2 ± 85.9	219.1 ± 96.7	253.8 ± 83.2	266.1 ± 76.5	315.5 ± 57.1	400.8 ± 50.3	330.0	<0.001*
Bleeding, ml	50.0	50.0	75.0 ± 35.4	100.0	115.0 ± 53.0	127.3 ± 51.8	283.3 ± 180.3	240.6 ± 215.4	416.7 ± 404.7	357.1 ± 430.9	427.3 ± 462.8	600.0 ± 244.9	800.0	0.030*
Conversion, yes/no	0/1	0/1	0/2	1/2	1/9	0/11	1/8	2/14	0/12	3/11	0/11	0/6	0/1	0.592
Transfusion, yes/no	0/1	0/1	0/2	0/3	0/10	0/11	0/9	1/15	3/9	3/11	1/10	5/1	0/1	<0.001*
POS, days	4.0	5.0	4.5 ± 2.1	6.7 ± 1.5	9.8 ± 5.0	10.7 ± 7.0	10.1 ± 2.5	11.6 ± 7.7	11.8 ± 7.1	11.6 ± 3.0	12.3 ± 3.6	15.2 ± 14.0	23.0	0.391
ALT, U/L	33.0	1138.0	183.5 ± 177.5	106.7 ± 36.1	220.3 ± 278.3	209.2 ± 180.1	292.9 ± 231.9	392.9 ± 370.7	345.8 ± 380.6	668.1 ± 743.8	414.6 ± 387.5	1002.7 ± 668.8	741.0	0.004*
AST, U/L	42	1088	204 199.4	142 ± 90.8	226.6 ± 335.6	207.2 ± 174.9	318.3 ± 247.6	371.5 ± 315.7	338.3 ± 406.4	508.1 ± 412.8	395.1 ± 275.6	876.8 ± 559.1	629	0.012*
TB, umol/L	14.8	72.5	11.5 ± 3.3	18.3 ± 4.1	18.2 ± 6.7	25 ± 21.5	17.9 ± 5.1	20.7 ± 11.3	18.2 ± 7.7	20.4 ± 7.8	23.5 ± 19.3	30.9 ± 13.5	21.3	0.026*
WBC, *10^9/L	12	11.7	11 ± 3.1	10.7 ± 5.5	11.7 ± 3.6	11.9 ± 3.3	11.7 ± 4.2	12.4 ± 5.2	10.1 ± 3.6	13.7 ± 4.5	13.9 ± 4.3	12.1 ± 4.3	10	0.805
CRP, mg/L	1.5	8	24.9 ± 16.1	32.6 ± 24.6	42.5 ± 29.6	54.3 ± 45.9	18.6 ± 10.9	41.9 ± 46.9	47.4 ± 39.2	39.5 ± 43.5	51.4 ± 34.3	75.0 ± 52.0	3.6	0.415
Morbidity, yes/no	0/1	0/1	0/2	0/3	1/9	3/8	1/8	4/12	2/10	1/13	1/10	2/4	1/0	0.525

POS, postoperative stay; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; WBC, white blood cell count; CRP, C-reactive protein.
*Statistically significant.

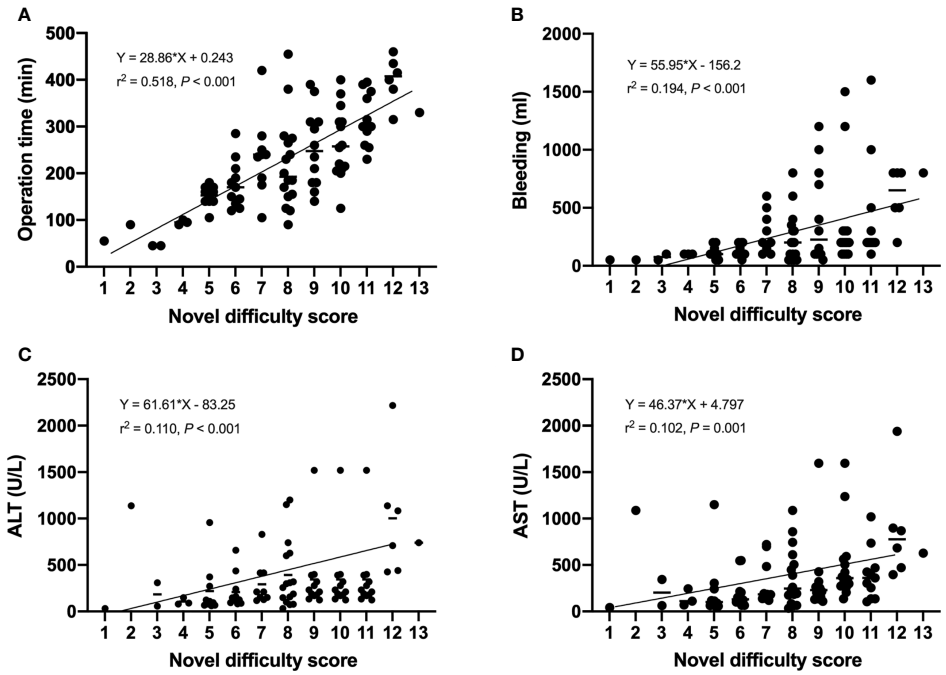

FIGURE 4
Operation time **(A)**, bleeding **(B)**, ALT **(C)**, and AST **(D)** according to difficulty score.

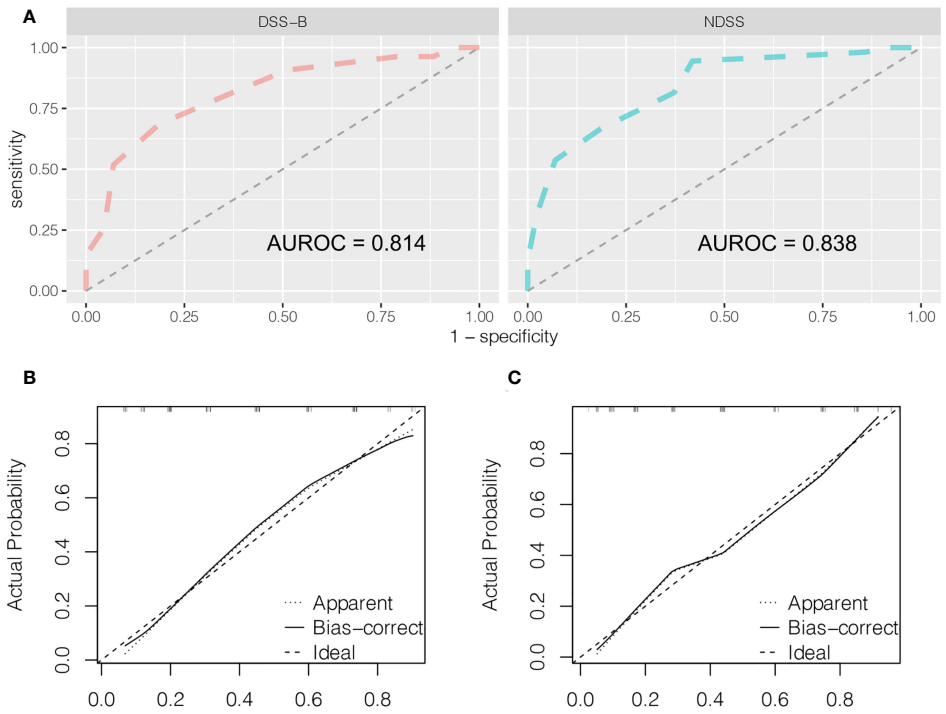

FIGURE 5
Predictive accuracy comparison of DSS-B and NDSS by ROC curve analyses **(A)**. The calibration curves for predicting surgical difficulty by DSS-B **(B)** and NDSS **(C)**.

TABLE 4 Surgical outcomes according to the novel difficulty scoring system (n=97).

Subgroup	Low (n=17)	Intermediate (n=48)	High (n=32)	*P* value
Operation time, min	119.4 ± 44.8	221.5 ± 84.8	310.3 ± 80.0	<0.001*
Bleeding, ml	100.0 ± 46.8	266.7 ± 264.2	440.6 ± 411.0	0.001*
Conversion, yes/no	2/15	3/45	3/29	0.746
Transfusion, yes/no	0/17	4/44	9/23	0.008*
POS, days	8.0 ± 4.5	11.1 ± 6.5	12.8 ± 6.7	0.041*
ALT, U/L	238.9 ± 320.6	320.3 ± 314.3	646.0 ± 629.9	0.002*
AST, U/L	248.8 ± 340.9	315.6 ± 302.3	542.2 ± 420.1	0.006*
TB, umol/L	20.4 ± 14.6	20.5 ± 12.8	23.5 ± 13.8	0.599
WBC, *10^9/L	11.5 ± 3.5	11.6 ± 4.2	13.4 ± 4.3	0.456
CRP, mg/L	34.2 ± 27.4	41.8 ± 40.9	49.1 ± 43.0	0.444
Morbidity, yes/no	1/16	10/38	5/27	0.356

POS, postoperative stay; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; WBC, white blood cell count; CRP, C-reactive protein.
Subgroup: Low, score = 1-5; Intermediate, score = 6-9; High, score = 10-14.
*Statistically significant.

The treatment of malignant tumors requires radical excision, while benign tumors can be excised close to the tumor without worrying about positive margins. Moreover, malignant tumors are often accompanied by changes in liver texture, such as hepatocellular carcinoma, which is often accompanied by hepatitis, hepatic fatty degeneration, or alcoholic liver. These changes were not sufficient to cause significant liver function damage and affected Child-Pugh score but increased operation time during surgery. There was an overlap between patients with HOH and patients with HOL. So, we selected HOH, malignant and DSS-B to build the novel difficulty scoring system. The novel system was an improvement of the classical model DSS-B. And the novel system was better than DSS-B according to the ROC curve.

Although there was no correlation between surgical difficulty and postoperative complications in this study, some studies have shown that highly difficult LLR might increase the incidence of postoperative complications (9, 15). High difficult LLR may lead to longer operation time and more blood loss, resulting in a higher incidence of postoperative complications. In these patients, laparoscopic hepatectomy should be carefully determined and recommended only in high-volume centres with an experienced team. Thus, more difficult cases would be taken over by more qualified surgeons (19). In addition to postoperative complications, the relationship between the difficulty grade of laparoscopic liver resection for malignant tumor and the long-term outcomes is of great concern to scientists (20). A growing body of evidence indicates that

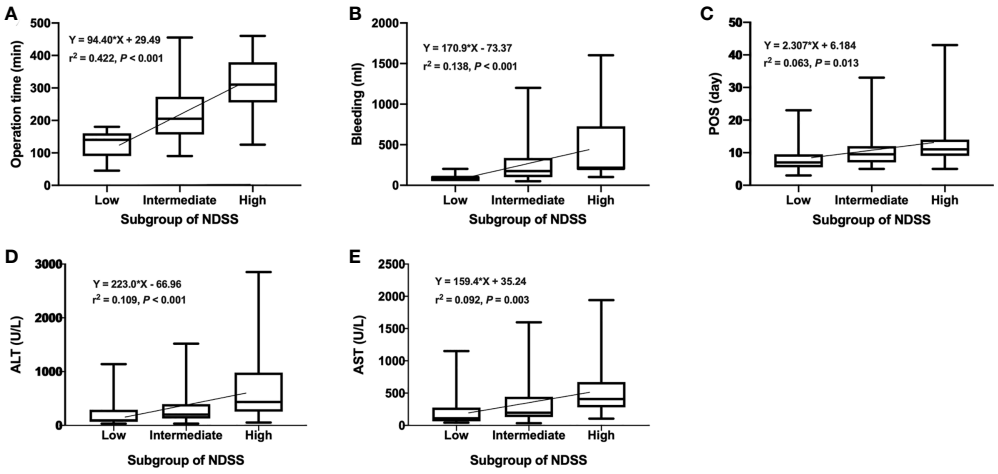

FIGURE 6
Operation time **(A)**, bleeding **(B)**, POS **(C)**, ALT **(D)**, and AST **(E)** according to subgroups.

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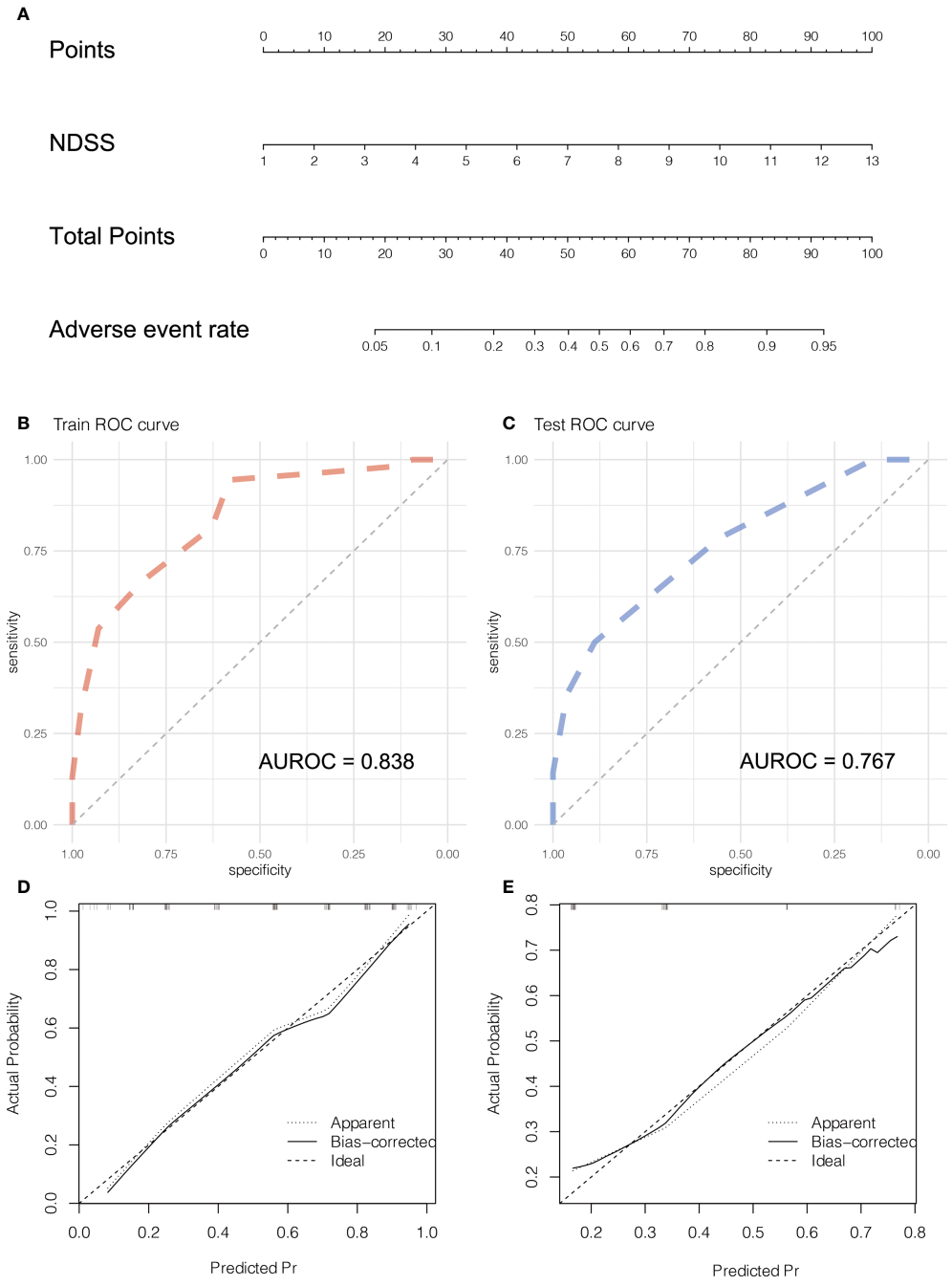

FIGURE 7
Development and validation the Nomogram of adverse event. The nomogram **(A)** of adverse event. The ROC curve of the nomogram in training **(B)** and testing **(C)** cohort. The calibration plots of the nomogram in training **(D)** and testing **(E)** cohorts.

postoperative complications, which in our series increased along with LLR difficulty, trigger the systemic proinflammatory cascade through the release of cytokines such as IL-1b, IL-6, TNF-a, oxidative stress, and immunosuppression and consequently promote tumorigenesis and metastatic spread (21–23). Postoperative complications have a negative impact on overall survival and disease-free survival in all types of malignancies (24, 25). In addition, failure or delayed administration of adjuvant therapy due to postoperative complications may increase tumor recurrence and affect survival. In addition, with the increase of LLR difficulty, the significant increase in intraoperative blood loss and transfusion

TABLE 5 Patient characteristics and surgical outcomes of LLR between Training and Testing cohorts.

Characteristic	Training group (97)	Testing group (41)	*P* value
Age, years	57.7 ± 12.6	58.9 ± 12.8	0.610
Gender, male/female	61/36	24/17	0.631
Hypertension, yes/no	31/66	16/25	0.424
Diabetes, yes/no	17/80	10/71	0.089
HOH, yes/no	16/81	2/39	0.115
POS, days	11.2 ± 6.4	9.4 ± 3.7	0.221[#]
Child-Pugh, A/B	95/2	38/3	0.312[$]
Tumor size, mm	47.3 ± 29.7	40.0 ± 24.2	0.531
NDSS, L/I/H[a]	26/30/31	2/33/6	0.765[&]
Pringle, yes/no	82/15	33/8	0.560
Operation time, min	232.9 ± 101.3	210.0 ± 77.89	0.199
Bleeding, ml	294.8 ± 321.4	206.2 ± 371.8	0.160
Transfusion, yes/no	13/84	2/39	0.242[$]
Conversion, yes/no	8/73	1/40	0.264[$]
Malignant, yes/no	72/25	21/20	0.008*
Postoperative morbidity	16/81	2/39	0.115[$]
Hemorrhage, yes/no	1/96	0/41	n.s[†]
Bile leakage, yes/no	4/93	1/40	0.989[$]
Ileus, yes/no	1/96	0/41	n.s[†]
Pneumonia, yes/no	3/94	0/41	0.555[†]
Pleural effusion, yes/no	3/94	2/39	0.989[$]
Abdominal infection, yes/no	2/95	0/41	n.s[†]
Liver failure, yes/no	1/96	0/41	n.s[†]
Incision infection, yes/no	2/95	0/41	n.s[†]
Postoperative day 1 (POD1)			
ALT, U/L	413.5 ± 470.5	215.7 ± 338.0	<0.001[#]*
AST, U/L	378.6 + 367.4	195.0 + 250.2	<0.001[#]*
TB, umol/L	21.5 ± 13.4	21.7 ± 7.5	0.106[#]
WBC, *10^9/L	12.1 ± 4.2	10.8 ± 3.5	0.065
CRP, mg/L	42.9 ± 39.6	25.7 ± 10.0	0.308[#]

HOH, history of hepatobiliary surgery; POS, postoperative stay; NDSS, novel difficulty scoring system; n.s, not significant; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; WBC, white blood cell count; CRP, C-reactive protein.
*Statistically significant; [#]Mann-Whitney test; [$]Chi-square with Yates' correction; [&]Chi-square test for trend; [†]Fisher's exact test.
[a]L, low (1-5); I, intermediate (6-9); H, high (10-14).

ratio was also a risk factor for poor short-term and long-term prognosis of various malignant tumors (26).

In addition to liver tumors, laparoscopic liver resection can also be used for intrahepatic duct (IHD) stones. Kim et al. developed a modified difficulty scoring system for IHD stones (10). The technical requirements of laparoscopic hepatectomy for IHD stones appear to be higher than for tumors, as the liver inflammation associated with IHD stones can lead to perihepatic adhesion and anatomic distortion. In addition, additional choledochoscopy of the remaining biliary tract is often required intraoperatively, which increases surgical complexity and prolongs surgical time. Therefore, under the same circumstances, laparoscopic liver resection for IHD stones is more difficult than liver tumors, and the two are not applicable to the same difficulty scoring system.

The use of surgical robots in liver surgery is growing almost daily. The robot offers a three-dimensional image with instruments of seven degrees of freedom (27). Compared with laparoscopic surgery, the main advantages of the robot are its ergonomic design, superior flexibility and visualization, which may better simulate open surgery and solve some operational difficulties in laparoscopic hepatectomy. However, the robotic hepatectomy is still a cutting-edge technology for liver surgeons, which requires a certain learning process. It is not clear whether the previous difficulty scoring system is suitable for robotic hepatectomy. Therefore, Chong et al. validated the DSS-B in robotic hepatectomy and to compare the outcomes of robotic hepatectomy and conventional laparoscopic hepatectomy among different difficulty levels (28). The results suggest that the benefits of the robotic platform may be minimal in

moderate-to-low difficulty hepatectomy. However, robotic approaches make high difficulty liver resection more minimally invasive.

There are multiple advantages to the present study. Firstly, history of previous abdominal surgery was included in the evaluation system of surgical difficulty of LLR. Additionally, this study is the first to develop a nomogram related to the difficulty of laparoscopic hepatectomy. However, the limitations of this study include its retrospective nature, and the lack of subgroup analysis of malignancies. The liver texture of hepatocellular carcinoma is different from that of metastatic liver tumors. In addition, some studies have shown that preoperative neoadjuvant chemotherapy also has a certain impact on liver resection for metastatic liver cancer, which was not reflected in this study (20, 29).

Conclusion

In conclusion, we improved the DSS-B and proposed a new classification system of LLRs according to their surgical difficulty. This system provides 3 difficult levels of LLRs: low difficulty, intermediate difficulty, and high difficulty. This classification could more accurately reflect the difficulty of surgery and help liver surgeons to make the surgical plan and ensure the safety of the operation. As surgeons gain experience, they can choose appropriate patients and gradually progress from a low level of expertise to an advanced level of expertise.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Affiliated Hospital of Jiangnan University ethics committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

CX and MZ: Study design, Data collection, Writing. TJ and YT: Study design, Data collection, Revision. LZ, ZY and ZZ: Study design, Data analysis. LX and ZL: Study design and Data analysis. WD, XX and WX: Study design, Data collection, Data analysis, Writing, Revision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Clinical application of regional and intermittent hepatic inflow occlusion in laparoscopic hepatectomy

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Aim: The aim of this study is to investigate the advantages and disadvantages of regional and intermittent hepatic inflow occlusion in laparoscopic hepatectomy.

Methods: The clinical data of 180 patients who underwent laparoscopic liver surgery in Taizhou People's Hospital from 2015 to 2021 were analyzed retrospectively. The patients were divided into the regional occlusion group (n = 74) and the Pringle's maneuver occlusion group (n = 106) according to the technique used in the intraoperative hepatic inflow occlusion. The pre- and intra-operative indicators, postoperative recovery indicators, and complications of the two groups were compared.

Results: There were no significant differences ($p > 0.05$) between the groups in terms of sex, age, preoperative alanine aminotransferase (ALT), preoperative aspartate aminotransferase (AST), preoperative albumin, alpha-fetoprotein, liver cirrhosis, hepatitis B, tumor location, gas embolism, intraoperative blood transfusion, postoperative albumin, postoperative total bilirubin (TBIL), postoperative hospital stays, and complications. The preoperative TBIL and operation time were higher in the regional occlusion group than in the Pringle's maneuver occlusion group, while the amount of intraoperative bleeding, postoperative ALT, and AST in the regional occlusion group were significantly lower than those in the Pringle's maneuver occlusion group ($p < 0.05$).

Conclusion: The two occlusion techniques are equally safe and effective, but regional hepatic inflow occlusion is more advantageous in operation continuity, intraoperative bleeding, and postoperative liver function recovery. The long duration and high precision of the regional blood flow occlusion technique demands a more experienced physician with a higher level of operation; therefore, it can be performed by experienced laparoscopic liver surgeons.

KEYWORDS

laparoscopic hepatectomy, liver surgery, Pringle's maneuver occlusion, regional occlusion, intraoperative bleeding

Introduction

Since the first laparoscopic liver resection was performed in 1991, the application of laparoscopic techniques in liver surgery has gradually unfolded, and laparoscopic liver resection has the advantages of less bleeding, less trauma, and faster recovery for almost all types of liver resection (1), ranging from partial hepatectomy to liver transplantation (2). Currently, the scope of surgery has evolved from the initial partial hepatectomy to the current accurate lobe hepatectomy and segmental hepatectomy (3).

The most dangerous complications of laparoscopic hepatectomy are massive hemorrhage and CO_2 gas embolism (4). Massive hemorrhage during a surgical operation will increase postoperative morbidity and mortality and is a major reason for conversion from laparoscopy to open surgery (5). Hepatic inflow occlusion is an effective method to control bleeding during hepatectomy. The most commonly used technique is the total hepatic inflow occlusion (Pringle's maneuver) (6). Pringle's maneuver was first described in 1908. It has the characteristics of wide application, simple operation, and favorable occlusion effect, but its disadvantages have also been noticeable. The occlusion of all hepatic blood flow into the first hepatic hilum with intermittent clamping and release is required for Pringle's maneuver. Thus, the continuity of the operation is interrupted, and bleeding of the hepatic cutting surface is increased significantly during the intermittent period. With the development of surgical technology, the application of regional occlusion has increased. Regional occlusion only blocks blood supply in the liver segment, does not affect the blood supply in the remnant liver, ensures the continuity of the operation, and reduces the amount of intraoperative bleeding. However, a demanding surgical technique is required for regional occlusion. At present, the regional occlusion approaches mainly include the intraglissonian and extraglissonian approaches. Both approaches can block the corresponding blood flow of the hepatic lobe or segment to achieve the purpose of accurate segmental hepatectomy. Some of the liver centers not only occlude hepatic blood flow into the first hepatic hilum, but also further dissect and block the hepatic vein at the second hepatic hilum to further reduce the incidence of surgical bleeding and CO_2 embolism.

The first hepatic hilum contains many blood vessels and bile ducts, where the space is narrow, and the anatomical structure is complex. If the surgeon is not careful enough to deal with the small branches of the portal vein during the surgical operation, it can result in uncontrollable bleeding and increase the incidence of complications. Thus, we explored the feasibility of the regional inflow occlusion technique by retrospectively comparing and analyzing the surgical results of the Pringle's maneuver and the regional inflow occlusion technique.

Materials and methods

General data: The clinical data of patients who underwent laparoscopic liver surgery of all types in Taizhou People's Hospital from 2015 to 2021 were retrospectively analyzed. The patients included 101 men and 79 women with a mean age of 56.04 ± 12.44 years, all with preoperative liver function scores of Child–Pugh A–B and the final diagnosis was confirmed by postoperative pathology.

Patient inclusion criteria: (1) preoperative imaging confirmed as a liver disease; (2) preoperative liver function score was Child–Pugh class A or B; (3) postoperative pathological diagnosis of liver disease; (4) no combined surgery involving other organs; and (5) no history of open upper abdominal surgery. Patient exclusion criteria: (1) tumor invading the hilar area of the liver; (2) comorbid severe cardiopulmonary disease; (3) comorbid hematological disease; and (4) conversion from laparoscopy to laparotomy.

Surgical procedure: (1) When the pneumoperitoneum pressure was stabilized to 12 mmHg, a 12-mm trocar was inserted into the abdominal cavity through a subumbilical longitudinal incision. A 5-mm trocar was placed at the intersection of the left midclavicular line and the transverse umbilical line, and another 5-mm trocar was positioned at the intersection of the left midclavicular line and subcostal margin line for assistance. A 5-mm trocar immediately subcostal in the right midclavicular line and a 12-mm trocar in the right midclavicular line were established as the main operation ports. The exact position was adjusted according to the patient's size, the size of the liver, and the location of the liver resection. (2) The perihepatic ligament was severed, and the ligamentum teres hepatitis, falciform ligament, left coronary ligament, and left triangular ligament were cut off in turn; thereafter, the right coronary ligament and hepatorenal ligament were severed. (3) Hepatic inflow occlusion: (a) Regional hepatic inflow occlusion: First, the proper hepatic artery and portal vein were dissected, and the arteries and veins of each hepatic lobe were dissected along the proper hepatic artery and portal vein. It is worth noting that some patients have a middle hepatic artery, which should be carefully identified during the surgical operation to avoid poor occlusion effects. In addition, before dissecting hepatic artery branches and portal vein branches, it is necessary to confirm the existence of other hepatic artery and portal vein branches to avoid injuries due to vascular variations in some patients. (b) Pringle's maneuver: The hepatoduodenal ligament was dissected, exposed, and routinely clamped using a tape for 15 min every period, and then released for a 5-min interval.

Diagnostic criteria for CO_2 gas embolism: Intraoperative monitoring of patient vital signs included the arterial oxygen saturation (SPO_2) measured by finger pulse oximetry and the partial pressure of end-tidal CO_2 ($PETCO_2$). CO_2 gas embolism was diagnosed if the patient had a rapid drop in $PETCO_2$, a drop in blood pressure when severe, a rapid increase in heart rate, or even a drop in oxygen saturation.

Statistical analysis: SPSS 19.0 software was used for statistical analysis. Measurement data with a normal distribution were presented as mean ± standard deviation (SD). Statistical differences were determined using analyses of variance or Student's *t*-tests. The qualitative data were analyzed using the Chi-square and Fisher's exact test. Differences were considered statistically significant when $p < 0.05$.

Results

The comparison of disease composition between two groups of patients

To study the relationship between clinical indicators and surgery-related outcomes of patients,180 patients with various types of liver diseases were included in this study, including 91 cases of hepatocellular carcinoma (HCC), 8 cases of hepatolithiasis, 37 cases of hepatic hemangioma (HH), 11 cases of focal nodular hyperplasia (FNH), 6 cases of metastatic hepatic carcinoma, 13 cases of intrahepatic cholangiocarcinoma (ICC), 4 cases of hepatic adenoma, 3 cases of inflammatory pseudotumor, 2 cases of coagulative necrosis, 2 cases of inflammatory myofibroblastic tumor of the liver (IMT), and 3 cases of intrahepatic choledochal cyst. A detailed information is presented in Table 1. There was no significant difference in disease composition between the two groups ($p > 0.05$).

TABLE 1 The comparison of the disease composition of patients between groups with different inflow occlusion techniques.

LLR

	Regional occlusion (n = 74)	Pringle's maneuver occlusion (n = 106)	χ^2	p-value
Diagnosis			9.709	0.452
HCC	35	56		
Hepatolithiasis	6	2		
HH	13	24		
FNH	6	5		
ICC	5	8		
Hepatic adenoma	3	1		
Metastatic hepatic carcinoma	2	4		
Inflammatory pseudotumor	2	1		
IMT	1	1		
Coagulative necrosis	0	2		
choledochal cyst	1	2		

The comparison of preoperative conditions between the two groups

A total of 180 patients were retrospectively analyzed, including 101 men and 79 women, with an average age of 56.04 ± 12.44 years. The patients were divided into two groups: the regional hepatic inflow occlusion group (n = 74) and Pringle's maneuver occlusion group (n = 106). A statistical analysis of sex, age, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), alpha-fetoprotein (AFP), hepatitis B surface antigen, and liver cirrhosis between the two groups was performed. There were no significant statistical differences in the general information of the patients except in preoperative TBIL between the two groups, as presented in Table 2.

The comparison of intraoperative conditions between the two groups

To analyze and compare the surgical outcomes of the two surgical approaches, statistical analysis was performed on the perioperative general characteristics of patients, including tumor location, operative time, hemorrhage, blood transfusions, and gas embolism in this study. The results revealed that the operative time in the regional occlusion group was longer than that in the Pringle's maneuver occlusion group (239.23 ± 96.26 vs. 204.93 ± 89.62 min), the difference was statistically significant (t = 2.450, p = 0.015), and the amount of intraoperative bleeding was less in the regional occlusion group than in the Pringle's maneuver occlusion group (209.05 ± 181.28 vs. 292.92 ± 309.69 ml, t = 2.284, p = 0.024). There was no occurrence of gas embolism in the regional hepatic inflow occlusion group, while there were two cases in the Pringle's maneuver occlusion group with no statistically significant difference between the two groups (χ^2 = 0.217, p = 0.641). One case of CO_2 gas embolism was caused by intraoperative injury to the short hepatic vein. In the other case, gas embolism was derived from the "aspiration" of air bubbles into the right atrium through the fissure of the injured hepatic vein into the inferior vena cava after the opening of the sieve-plate fenestrae in the middle hepatic vein of the hepatic cutting surface due to asynchronous blockage of the hepatic venous system. The surgeon alleviated CO_2 embolism by reducing pneumoperitoneum pressure, clamping the short hepatic vein, and suturing the sieve-plate fenestrae of the

TABLE 2 The comparison of preoperative conditions between the two groups of patients with different inflow occlusion techniques.

LLR

	Regional occlusion (n = 74)	Pringle's maneuver occlusion (n = 106)	t/χ^2	p-value
Age (years)	54.99 ± 13.66	56.78 ± 11.52	0.953	0.342
Sex			0.025	0.873
Men	41	60		
Women	33	46		
ALT (U/L)	45.85 ± 86.74	28.56 ± 22.34	1.676	0.098
AST (U/L)	39.48 ± 52.66	28.37 ± 13.39	1.777	0.079
AFP (ug/L)	100.98 ± 311.64	67.28 ± 236.03	0.825	0.410
Cirrhosis			0.737	0.391
Positive	24	41		
Negative	50	65		
TBIL (μmol/L)	18.03 ± 9.61	14.34 ± 5.71	2.960	0.004
ALB (g/L)	40.28 ± 6.70	41.40 ± 4.65	1.332	0.185
HbsAg			0.450	0.502
Negative	49	65		
Positive	25	41		

middle hepatic vein. The comparison of intraoperative conditions between the two groups is presented in Table 3.

The comparison of postoperative recovery indicators between the two groups

Liver function was re-examined on the third postoperative day to compare the intraoperative liver function damage and postoperative recovery of liver function between the two groups. We observed that ALT and AST levels were lower in the regional hepatic inflow occlusion group than in the Pringle's maneuver occlusion group, while no statistically significant difference was observed in TBIL, albumin, and hospital days, as presented in Table 4.

The comparison of postoperative complications between the two groups

The major surgical complications of laparoscopic liver surgery include postoperative abdominal hemorrhage, bile leakage, fever, incisional infection, and ascites. Four patients in each group had bright red bloody fluid draining from the abdominal drainage tube after surgery, but all improved after

TABLE 3 The comparison of the intraoperative conditions of patients between groups with different inflow occlusion techniques.

LLR

	Regional occlusion (n = 74)	Pringle's maneuver occlusion (n = 106)	t/χ^2	p-value
Tumor location			6.341	0.096
Left lateral lobe	31	31		
Left inner lobe	11	10		
Right anterior lobe	14	34		
Right posterior lobe	18	31		
Operative time (min)	239.23 ± 96.26	204.93 ± 89.62	2.450	0.015
Blood loss (ml)	209.05 ± 181.28	292.92 ± 309.69	2.284	0.024
Blood transfusions (U)	0.33 ± 1.15	0.34 ± 1.14	0.077	0.939
Gas embolism			0.217	0.641
Negative	74	104		
Positive	0	2		

TABLE 4 The comparison of liver function at 3 days after surgery and postoperative hospitalization days between the two groups of patients.

LLR

	Regional occlusion (n = 74)	Pringle's maneuver occlusion (n = 106)	t/χ^2	p-value
ALT (U/L)	105.70 ± 87.63	150.61 ± 171.95	2.066	0.040
AST (U/L)	56.05 ± 64.15	82.55 ± 91.05	2.290	0.023
Albumin (g/L)	35.96 ± 4.06	35.41 ± 4.33	0.862	0.390
Total bilirubin (μmol/L)	20.36 ± 9.57	20.17 ± 14.92	0.098	0.922
Postoperative hospitalization days	9.55 ± 3.55	9.55 ± 3.55	0.203	0.839

conservative treatment and did not undergo reoperation. Two cases of ascites, one case of incisional infection, one case of fever, and two cases of bile leakage were observed in the regional occlusion group. One of the two patients with bile leakage had hepatocellular carcinoma, and no bile leakage was identified during intraoperative examination with the use of gauze swabs, but the bile leakage occurred after surgery. The other patient had hepatolithiasis, and the bile leakage also occurred after surgery. Five cases of ascites, one case of incisional infection, and five cases of fever occurred in the Pringle's maneuver occlusion group, and no postoperative bile leakage occurred. There were no statistically significant differences in postoperative complications between the two groups (χ^2 = 0.111, p = 0.739), and all patients were discharged smoothly, as presented in Table 5.

Discussion

Hepatectomy is still the first choice of treatment for benign and malignant liver tumors and hepatolithiasis. In recent years, with the further understanding of liver anatomy and the continuous development of laparoscopic techniques, laparoscopic hepatectomy has received increasing attention, and a history of upper abdominal surgery is no longer considered a contraindication to laparoscopic hepatectomy (7). Early laparoscopic hepatectomies were mostly localized resections of the margins or surface of the liver, and few anatomical resections were performed, and dissection of the portal vein and hepatic vein trunk was generally not required intraoperatively. Currently, with the development of technology, liver resection is now in the era of precise hepatectomy. Laparoscopy is also gradually being used in extensive hepatectomy or difficult hepatectomy (8). On one hand, the portal vein and hepatic vein are often exposed during liver surgery, and the operations of hemostasis and suture are more difficult in laparoscopic surgery than in laparotomy due to the limited operating space. On the other hand, CO_2 pneumoperitoneum needs to be maintained for a long time, leading to gas embolism. Therefore, the two major risks of laparoscopic hepatectomy are bleeding and CO_2 gas embolism.

TABLE 5 The analysis of postoperative complications in the two groups.

	Regional occlusion	Pringle's maneuver occlusion	χ^2	p-value
Total postoperative Complication	16	25	0.228	0.954
Clavien I–II	13	21		
Clavien III–IV	3	4		
Abdominal hemorrhage	4	4		
Bile leakage	2	0		
Fever	1	5		
Incisional infection	1	1		
Ascites	2	5		
Abdominal hemorrhage + Incisional infection + Ascites	0	1		
Bile leakage + Abdominal hemorrhage	1	0		

Studies have shown that the incidence of conversion from laparoscopy to laparotomy due to uncontrollable intraoperative bleeding is 6%–11% (9). To reduce and control bleeding during hepatectomy, a variety of hepatic inflow occlusion techniques have been clinically used. Pringle's maneuver is the most commonly used occlusion technique at present, with a favorable effect and a hassle-free procedure, which can be used in almost all types of hepatectomy. There are many ways of occlusion with this technique. In most patients with no adhesion or dissociable adhesions around the hepatic hilum, the hepatoduodenal ligament can be dissected, and the surgeon can use the occlusion tape to encircle the hepatoduodenal ligament for occlusion. For some patients with hepatic hilar adhesions that cannot be dissected to create a space behind the hepatoduodenal ligament, the occlusion tape cannot be passed behind the hepatoduodenal ligament. In those cases, the same favorable occlusion effect can be achieved using the Satinsky vascular clamp (10).

Despite the favorable hemostasis effect of Pringle's maneuver, its disadvantages are noticeable as well: (1) The occlusion and subsequent restoration of hepatic blood flow

easily led to hepatic ischemia–reperfusion injury; the reperfusion can activate Kupffer cells through pathways of damage-associated molecular patterns, which induce oxidative stress and inflammatory response, ultimately leading to hepatocyte injury and apoptosis (11). Pringle's maneuver can also greatly increase systemic vascular resistance, increase pulmonary artery pressure and mean arterial pressure, reduce cardiac ejection fraction, and cause portal vein thrombosis after long-term occlusion (12). (2) Previous studies on Pringle's maneuver have revealed that in patients without liver disease and a hepatic inflow occlusion duration of less than or equal to 20 min or patients with liver disease and a hepatic inflow occlusion duration of less than or equal to 10 min followed by 5 min of reperfusion, the liver function can recover to its preoperative level within 1–3 days. Therefore, after every 20 or 10 min of inflow occlusion, 5 min of release is required, which interrupts the continuity of the operation.

In particular, the duration of occlusion would often be prolonged when the control of intraoperative bleeding is time-consuming. The occlusion interval for restoring the hepatic inflow is usually 5 min, during which the wound bleeds more. Therefore, the total amount of bleeding will increase significantly as the operation time is prolonged and the times of interval increase (13). (3) Some studies have revealed that the occlusion of hepatic inflow cannot only lead to the impairment of liver function, but can also result in functional damage to the target organs. This is because the blood in the gastrointestinal tract cannot return to the systemic circulation through the portal vein, causing damage to the intestinal mucosal barrier and the subsequent translocation of bacterial endotoxin to extra-intestinal organs, which leads to the release of inflammatory mediators from immune cells to the target organs (14) (15) (16).

Regional inflow occlusion has been gradually applied to avoid the disadvantages of total hepatic inflow occlusion. More surgeons are now using regional hepatic inflow occlusion for laparoscopic liver surgery. The liver lobe vessels to be resected are dissected and occluded, followed by the hepatectomy. This technique can not only avoid the ischemia–reperfusion injury of the remnant liver, but also assure an unrestricted operation period and the continuity of the surgery. In this study, the postoperative liver function was better in the regional hepatic inflow occlusion group than in the Pringle's maneuver occlusion group, but the surgical difficulty and complexity of the former are much higher than that of the latter, and experienced surgeons are needed to reduce the occurrence of complications.

There are some controversies about regional hepatic inflow occlusion. The regional occlusion approaches mainly include the intraglissonian and extraglissonian approaches. The intraglissonian approach was adopted in this study, in which the surgeon needs to open Glisson's sheath, dissect the portal vein branches and hepatic artery branches, and block them. This is a demanding surgical operation, during which hemorrhage often occurs when the surgeon forcibly dissects the adhesions in Glisson's sheath. However, with the development of the technique, more surgeons have been able to master this technique. Previously, surgical operation by the extraglissonian approach often led to the impairment of the hepatic parenchyma, which was prone to intraoperative bleeding and affected the laparoscopic view and operation. In recent years, with histological confirmation of the existence of the Laennec membrane, surgeons have been performing the extraglissonian occlusion through the Laennec membrane, to avoid the complex dissection of Glisson's sheath and reduce the damage to the liver parenchyma (17). Some surgeons use simultaneous fluorescence-guided laparoscopy to perform hepatectomy, allowing more precise hepatectomies.

The main complications of laparoscopic hepatectomy are bleeding and CO_2 embolization. In the Pringle's maneuver occlusion group, the bleeding on the liver resection surface increases significantly due to repeated release of occlusion. In this study, the intraoperative bleeding was less in the regional occlusion group than in the Pringle's maneuver occlusion group (209.05 ± 181.28 vs. 292.92 ± 309.69 ml, $t = 2.284$, $p = 0.024$). Compared with the Pringle's maneuver occlusion group, the regional occlusion group only occluded the inflow of the operation area without affecting the blood supply of the remnant liver. There was no increase in bleeding of the hepatic cutting surface during the occlusion interval. Intraoperative operations may lead to the compression of the inferior vena cava, causing an increased blood flow rate and decreased pressure on the side wall of the blood vessel. This easily creates the Venturi effect that drives the aspiration of CO_2 from the abdominal cavity into the circulation (18). The rapid accumulation of CO_2 in the circulation can cause hypoxemia and acidosis. In serious cases, gas accumulation in the cardiac cavity results in pulmonary artery thrombosis, which is very risky. There was no significant difference in the incidence of CO_2 embolism between the two groups in this study, because the hepatic venous system was not occluded in any occlusion techniques. During the operation, the dissection of the liver segment required the exposure of the hepatic vein. The wall of the hepatic vein is thin with many identified sieve-plate fenestrae. The vascular sieve-plate fenestrae can be easily exposed during the operation, resulting in bleeding and CO_2 embolism. In case of CO_2 embolism during operation, if the sieve-plate fenestra is small, it can be closed by applying absorbable hemostatic gauze or bipolar electrocoagulation. If the sieve-plate fenestra is large, it is necessary to reduce the pneumoperitoneum pressure and suture it, to control the bleeding or CO_2 embolism effectively. In addition, the operation time was longer in the regional occlusion group than in the Pringle's maneuver occlusion group (239.23 ± 96.26 vs. 204.93 ± 89.62 min, $t = 2.450$, $p = 0.015$), and the operator must carefully dissect each portal vein branch, hepatic artery branch, and bile duct branch in the first hepatic portal

area before occluding the hepatic inflow area; therefore, the required operation time is prolonged.

Postoperative liver function is also an important indicator to evaluate the effect of the surgery. Some studies have revealed that regional hepatic inflow occlusion has a better protective effect on liver function in laparoscopic hepatectomy than Pringle's maneuver. In this study, the results of ALT and AST of patients are better in the regional occlusion group than in the Pringle's maneuver occlusion group on the third day after the operation, which is consistent with the results of other studies. The TBIL of patients in the regional occlusion group was higher than that of patients in the Pringle's maneuver occlusion group before the operation, but there was no significant difference between the two groups after an operation, which showed that the TBIL recovery of patients in the regional occlusion group was better than that in the Pringle's maneuver occlusion group.

There were many postoperative complications in liver surgery, and there were no significant differences in the occurrence of various complications between the two groups (10 vs. 15, $\chi^2 = 0.111$, $p = 0.739$). Among them, postoperative bile leakage (POBL) is one of the main complications, with an incidence of about 3.6%–11% (19), and POBL will have an impact on the postoperative course (20). A study included 13,379 patients who underwent laparoscopic hepatectomy or open hepatectomy, in which the incidence of POBL in laparoscopic hepatectomy was lower than that in open hepatectomy (21). There are many reasons for the occurrence of bile leakage. First, some intraoperative bile leakage locations are difficult to operate under laparoscopy; therefore, it is impossible to close the bile duct effectively. Second, some are delayed bile leakage that cannot be identified despite a careful inspection of the operator on the hepatic cutting surface during the operation. There were two cases of POBL in the regional occlusion group and one case of POBL in the Pringle's maneuver occlusion group, and all of them had hepatolithiasis, which may be related to local inflammation of the bile duct (22), bile duct dilatation, or ineffective coagulation of the bile duct by an ultrasonic knife. Bile leakage can cause infection; the bacterial culture of abdominal drainage fluid from the patient was positive, indicating abdominal infection. The patient was cured after puncture drainage and was discharged smoothly. There were more than 100 ml of bright red drainage fluid in the drainage tube of eight patients in the two groups after an operation. After applying hemostatic medication and prothrombin complex, all the patients were discharged smoothly. Moreover, complications were also related to the operator's experience in laparoscopic hepatectomy.

In conclusion, this study suggests that Pringle's maneuver is suitable for patients with a small hepatic cutting surface after resection and anticipated short operation time. Regional hepatic inflow occlusion has the advantages of better continuity of the operation, less intraoperative hemorrhage, and less damage to liver function. The long duration and high precision of the regional hepatic inflow occlusion technique demands a more experienced physician with a higher level of operation; therefore, it can be performed by experienced laparoscopic liver surgeons.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

LS and XL conceived and designed the study as well as drafted the manuscript. BL and YM collected the data. YY and DS conducted the statistical tests. QZ made language changes. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Counterclockwise modular laparoscopic anatomical mesohepatectomy using combined glissonean pedicle (Takasaki approach) and hepatic vein-guided approaches

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Background: Although laparoscopic anatomical hepatectomy (LAH) is widely adopted today, laparoscopic anatomic mesohepatectomy (LAMH) for patients with hepatocellular carcinoma (HCC) remains technically challenging.

Methods: In this study, 6 patients suffering from solitary liver tumors located in the middle lobe of the liver underwent counterclockwise modular LAMH using combined Glissonean pedicle (Takasaki approach) and hepatic vein-guided approaches. In this process, the Glissonean pedicle approach (Takasaki approach) was first used to transect the liver pedicles of segment right anterior (G58) and segment 4 (G4). Second, the hepatic vein-guided approach was performed along the umbilical fissure vein (UFV) to sever the liver parenchyma from the caudal to cranial direction, and the middle hepatic vein (MHV) and anterior fissure vein (AFV) were then disconnected at the root. Last, the hepatic vein-guided approach was once more performed along the ventral side of the right hepatic vein (RHV) to transect the liver parenchyma from the cranial to anterior direction, and the middle lobe of the liver, including the tumor, was removed completely. The entire process was applied in a counterclockwise fashion, and the exposure or transection sequence was G58, and G4, followed by UFV, MHV, AFV, and finally, the liver parenchyma along the ventral side of RHV.

Results: The counterclockwise modular LAMH using combined Glissonean pedicle (Takasaki approach) and hepatic vein-guided approaches was feasible in all 6 cases. The median duration of the operation was 275 ± 35.07 min, and the mean estimated blood loss was 283.33 ml. All of the 6 patients recovered smoothly. The Clavien-Dindo Grade I-II complications rate was up to 33.33%, mainly characterized by postoperative pain and a small amount of ascites. No Clavien-Dindo Grade III-V complications occurred, and the mean

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postoperative hospital stay was 6.83 ± 1.47 days. Follow-up results showed that the average disease-free survival (DFS) was 12.17 months, and the 21-months OS rate, DFS rate and tumor recurrent rate were 100%, 83.33% and 16.67% respectively.

Conclusions: Counterclockwise modular LAMH using combined Glissonean pedicle (Takasaki approach) and hepatic vein-guided approaches takes the advantages of the two approaches, is a novel protocol for LAMH. It is thought to be technically feasible for patients with a centrally located solitary HCC. The oncologic feasibility of this technique needs to be investigated based on long-term follow-up. A multicenter, large-scale, more careful study is necessary.

KEYWORDS

hepatic, laparoscopic, anatomical hepatectomy, mesohepatectomy, surgical procedure

Introduction

Laparoscopic anatomical hepatectomy (LAH), together with open anatomical hepatectomy (OAH), is a hot topic in the liver surgical field and has been demonstrated to be an ideal curative treatment for hepatocellular carcinoma (HCC) (1). Compared to OAH, LAH has the advantages of small trauma, beautiful incision, rapid recovery, a short hospitalization time and light postoperative pain. In addition, LAH versus laparoscopic nonanatomical hepatectomy (LNAH) for selected HCC patients was shown to be associated with increased disease-free survival (DFS), a lower intrahepatic ipsilateral recurrence rate, and comparable long-term overall survival (OS) and postoperative complications (2). Thus, LAH is a popular procedure, and its indications are gradually expanding. However, the optimum approach to complete LAH has not yet been identified.

The Takasaki approach, the extrafascial Glissonean pedicle approach introduced by Takasaki in approximately 1986, is an approach to the pedicles at the hepatic hilus without liver dissection (3). When the hilar plate is pulled down after detaching the liver parenchyma, the right and left Glissonean pedicles can easily be approached (4). Thus, this approach was considered to be a simple and versatile application procedure to carry out LAH (5, 6).

The hepatic vein, a branch of the inferior vena cava running between hepatic segments or lobes and collecting blood from the liver parenchyma, is often used as an anatomical landmark and is continuously exposed on the plane of hepatic disconnection in OAH or LAH (7). Especially in LAH, the operator is often disoriented because of the visual field, so a path guided by the hepatic vein has become valuable (8).

Due to the complex structure of the central region of the liver, which involves the Glissonean pedicles of segment right anterior (G58) and segment 4 (G4), umbilical fissure vein (UFV), middle hepatic vein (MHV), anterior fissure vein (AFV) and the right hepatic vein (RHV), laparoscopic anatomic mesohepatectomy (LAMH) remains technically challenging in the clinic (9). To date, no standard surgical procedure for LAMH has been reported. Herein, we introduce some recent cases of counterclockwise modular LAMH using combined Glissonean pedicle (Takasaki approach) and hepatic vein-guided approaches, which may offer a benefit for difficult procedures.

Patients and methods

The study was approved by the Institutional Ethics Committee of Binzhou Medical University Hospital. All surgical procedures in the study were performed in accordance with the relevant regulations at our hospital. Informed consent of patients for surgery or invasive treatment was obtained separately before the operation.

Patient selection

In this study, consecutive patients who underwent LAMH using combined Glissonean pedicle (Takasaki approach) and hepatic vein-guided approaches for HCC from January 1, 2021, to May 31, 2022, at Binzhou Medical University Hospital were included. Patients with benign tumors or other types of malignant tumors and patients who underwent LNAH were excluded.

Perioperative care

All patients received preoperative laboratory tests, including routine blood, blood biochemical index, blood clotting, hepatitis B virus and HBV-DNA tests, if necessary. Child–Pugh classification and indocyanine green retention rate at 15 minutes (ICG-R15) were required, as patients suffering from LAMH are at risk of acute liver failure (ALF) after major hepatectomy. Only patients with a Child–Pugh grade A or B, estimated remnant liver volume >40%, and ICG-R15 <25% were allowed to undergo the protocol. A three-dimensional (3D) reconstruction model of the liver for each patient was also built by the IQQA-Liver system (EDDA Company, USA) using the preoperative computed tomography (CT) or magnetic resonance imaging (MRI) image, which could vividly visualize the target Glissonean pedicle (G58 and G4), main hepatic vein (UFV, MHV and AFV) and its important branches. Moreover, the system helps to measure the residual liver volume and the standard liver volume.

All patients received general anesthesia with a central venous pressure controlled at 2-5 cm H_2O. An experienced surgical team, including 3-4 surgeons, 1-2 anesthesiologists, and 1-2 instrument nurses, completed the operation together with or without indocyanine green fluorescence staining.

Postoperative management was relatively simple, including hepatinica treatment, rehydration, infection prevention, etc. Chest and abdominal CTs were required to be reviewed to assess for the presence of reactive pleural effusion and peritoneal encapsulated effusion after the operation.

Surgical procedure

All LAMH procedures were performed by the same surgical team. During the protocol, patients were placed in the supine position with legs apart under intravenous and inhalational anesthesia. Double main operator mode was performed, of which one main operator stood on the right side of the patient, and another main operator stood on the left, while the assistant holding the scope stood between the patient's legs. The pneumoperitoneum pressure was maintained at 10-14 mmHg, and the central venous pressure was maintained at 2-5 cm H_2O. Five ports were routinely needed, including one 10-mm observation port, two 12-mm operating ports, and two 5-mm assistant ports.

During the protocol, to avoid the spreading of malignant cells, the liver was freed from the ligamentum teres hepatis and falciform ligament without hard compression. Cholecystectomy was performed routinely, or the gallbladder was suspended after disconnecting the gallbladder duct and artery if the bottom or body was invaded by HCC, avoiding direct contact with the tumor. The Pringle maneuver was conducted extracorporeally and intermittently during the transection of the liver parenchyma with the "15-min clamping and 5-min release" principle.

The modular procedure began with the handling of the G58 using the Takasaki approach and hilar plate descending technique, and the entire process was then applied in a counterclockwise sequence. After approaching the target pedicles of G58, clips were used to test the clamp, and the Glissonean pedicles of G4 were then approached by dissecting the umbilical fissure. Usually, 3-4 branches of G4a and G4b were disconnected, and the UFV was exposed during this process. Negative fluorescent staining, through the injection of indocyanine green (ICG) (1 ml, 5 mg/L) from peripheral veins, helped to accurately disconnect the liver parenchyma, and blood flow into the middle liver had, in theory, been completely controlled at this time. If the demarcation line of the ICG fluorescence-negative regions, normally consistent with the ischemic line, was satisfactory, the target pedicles of G58 could be transected subsequently with an Endo&GIA (Johnson & Johnson Company, USA). The hepatic vein-guided approach was first performed along the trunk of the UFV to transect the liver parenchyma from the caudal to cranial direction, and the second porta hepatis was then easily reached. The MHV was subsequently transected at the root using Endo&GIA, followed by the transection of the AFV in the same manner. Both these procedures were completed by the first main operator standing on the right side of the patient. Another main operator on the left then completed subsequent procedures along the ventral side of the RHV to transect the liver parenchyma from the cranial to the caudal direction using a hepatic vein-guided approach, and the whole RHV trunk was exposed at the surgical plane. So far, the whole protocol has been completed, and the middle lobe of the liver, including the tumor, was removed completely. Concrete process was displayed schematically in Figure 1.

Data collection

All data were collected from our clinical database, including age, sex, body mass index (BMI), hepatitis B virus status, Child–Pugh class, ICG-R15, duration of operation, estimated intraoperative blood loss, and times of the Pringle maneuver; postoperative outcomes, such as levels of alanine aminotransferase (ALT) and glutamic oxaloacetic transaminase (AST) on the first day after the operation (POD1); postoperative length of hospital stay; and postoperative complications, classified according to the Clavien–Dindo classification, including abdominal dropsy, pleural effusion, postoperative intra-abdominal hemorrhage, bile leakage, and intra-abdominal infections (IAIs) were also collected. The duration of the operation, estimated intraoperative blood loss, and times of Pringle maneuver data were obtained from the anesthesia records. First-day levels of ALT and AST, the length of postoperative hospital stay, postoperative intra-abdominal hemorrhage data, bile leakage data, and IAI data were obtained from our clinical records. Follow-up was standardized using telephone and outpatient follow-up, and the MRI of upper abdomen was necessary in each outpatient follow-up to

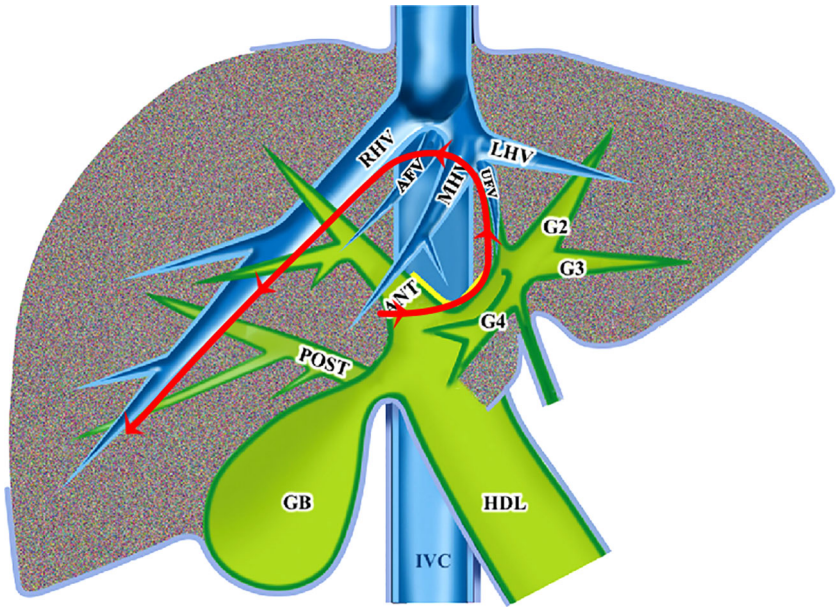

FIGURE 1
Program diagram of counterclockwise modular LAMH using combined Glissonean pedicle (Takasaki approach) and hepatic vein-guided approaches.

assess the tumor prognosis. The overall survival (OS) rate, tumor recurrent rate, disease-free survival (DFS) rate and the average DFS were recorded respectively.

Statistical analysis

Continuous variables are expressed as the mean and standard deviation (SD). The continuous and categorical variables were compared using ANOVA and Chi-squared tests, respectively. All analyses were performed with the Statistical Package for Social Sciences (SPSS) version 24.0 software (IBM Co, Armonk, NY, USA). Survival was evaluated using the Kaplan-Meier method.

Results

Patient characteristics

Seven LAMHs were performed in this study. One patient was excluded because she had no background of hepatitis B and cirrhosis, and the postoperative pathological examination revealed intrahepatic cholangiocarcinoma (ICC) rather than HCC. Therefore, 6 patients (4 males, 2 females) with a mean age of 54.50 years were included in the study and underwent the counterclockwise modular LAMH using combined Glissonean pedicle (Takasaki approach) and hepatic vein-guided approaches. The mean BMI of the 6 patients was 25.50 kg/m^2. All 6 patients had a history of hepatitis B virus and cirrhosis, but their Child–Pugh stages were classified as A or B, and the mean ICG-R15 (%) was 6.19. The demographic characteristics of the 6 patients are displayed in Table 1.

Surgical outcomes

All 6 counterclockwise modular LAMHs using combined Glissonean pedicle (Takasaki approach) and hepatic vein-guided

TABLE 1 Demographic characteristics of the included patients.

Parameter	*N=6*
Age (years)	54.50 ± 10.75
Gender	
Male	4 (66.67%)
Female	2 (33.33%)
BMI	25.50 ± 1.70
Underlying liver disease	
Hepatitis B	6 (100%)
Cirrhosis	6 (100%)
Stages of Child-Pugh	
A	4 (66.67%)
B	2 (33.33%)
ICG-R15 (%)	6.19 ± 1.70
Preoperative ALT (U/L)	49.25 ± 39.15
Preoperative AST (U/L)	52.10 ± 35.02
Tumor size in CT/MRI (cm)	5.17 ± 0.72

approaches went smoothly. The median duration of the operation was 275 ± 35.07 min, and the mean estimated blood loss was 283.33 ml. The overall postoperative recovery was relatively uneventful. The ALT and AST levels, had no significant elevation, were 285.10 ± 95.36 U/L (Normal Range: 15 - 40 U/L) and 265.57 ± 66.74 U/L (Normal Range: 9 - 50 U/L) respectively on POD1. The Clavien-Dindo Grade I-II complications rate was up to 33.33%, mainly characterized by postoperative pain and a small amount of ascites. No Clavien-Dindo Grade III-V complications, such as postoperative intra-abdominal hemorrhage, bile leakage, or IAI, even dead, occurred, and the mean postoperative hospital stay was 6.83 ± 1.47 days.

Follow-up checkups for 4 - 21 months (mean, 12.5 months). All patients survived in the last follow-up, but one case relapsed at the 13th month after operation, and transcatheter hepatic artery chemoembolization (TACE) followed by target therapy and immunotherapy were received then. The average DFS was 12.17 months, and the 21-months OS rate, DFS rate and tumor recurrent rate were 100%, 83.33% and 16.67% respectively. Details of the surgical outcomes are displayed in Table 2.

Discussion

Currently, laparoscopic mesohepatectomy, especially LAMH, remains a challenging procedure. Although the selection of appropriate patients and detailed preoperative evaluations, such as 3D visual structure reconstruction, help to ensure the success of the operation, an increased number of vessels in the middle hepatic lobe, multiple variations in the vessel course between the anterior and posterior regions, and a relatively narrow operating space under the diaphragm are all unfavorable factors restricting the protocol. Simplifying these complications is a critical topic faced by hepatobiliary surgeons.

TABLE 2 Details of surgical outcomes of the included patients.

Parameter	*N=6*
Estimated blood loss (ml)	283.33 ± 103.28
Patients transfused in PD	0
duration of operation (min)	275 ± 35.07
Times of Pringle maneuver	4.17 ± 1.17
ALT on POD1 (U/L)	285.10 ± 95.36
AST on POD1 (U/L)	265.57 ± 66.74
Postoperative hospital stay	6.83 ± 1.47
Complications	*2 (33.33%)*
Clavien-Dindo Grade I-II	*2 (33.33%)*
postoperative pain	1 (16.67%)
ascites	1 (16.67%)
Clavien-Dindo Grade III-V	*0*
postoperative intra-abdominal hemorrhage	0
bile leakage	0
IAI	0
OS rate	6 (100%)
DFS rate	5 (83.33%)
Tumor recurrent rate	1 (16.67%)
average DFS (month)	12.17

In 1985, Couinaud published a report on left hepatectomy with the extrafascial approach in *Surgery* (10), which is the predecessor and the earliest application of the Takasaki approach. In 1986, Takasaki presented a novel liver segmentation approach that divided the liver into three main parts and a caudate area according to the ramification of the Glissonean pedicles. On this basis, he published the extrafascial approach (Takasaki approach) in Japanese and reported that it can be used not only for the main portal pedicle but also for the sectional portal and segmental pedicles in the left and right liver (3, 4, 11–13). Therefore, various types of AH can be carried out with the Takasaki approach. Since the 1980s, this approach has provided new knowledge of surgical anatomy and techniques, and various types of AH have been safely achieved by the Takasaki approach (6, 14, 15). Furthermore, the Takasaki approach, used in AH or LAH, has also been demonstrated to have a potential oncology clinical benefit (16, 17).

Nevertheless, the Takasaki approach without liver dissection could be better utilized. To this end, the existence of Laennec's capsule needs to be recognized. Laennec's capsule can be separated from Glisson's capsule outside and inside the liver, including the main portal pedicles as well as the sectional and segmental pedicles, and can be approached at the hepatic hilus (18). Because of the existence of Laennec's capsule, the Glissonean pedicles can be easily and safely separated by blunt separation rather than by an incision of the liver parenchyma, thus facilitating the Takasaki approach in AH or LAH. Many related studies have also demonstrated that Laennec's approach based on Laennec's capsule can contribute to the standardization of the surgical technique for LAH and bring innovations that facilitate safe and effective liver resection under laparoscopy (19–21).

As described previously, the hepatic vein is the boundary of the Couinaud segment; thus, it is often used as an anatomical landmark in OAH or LAH. Continuous exposure on the plane of hepatic disconnection is usually regarded as a successful sign for OAH or LAH. However, its isolation and exposure is a high-risk procedure, and a slight mistake might lead to massive bleeding or other serious consequences and require converting to an open procedure. In current practice, the hepatic vein approach can be subdivided into the caudal approach, caudal-dorsal approach, cranial-ventral approach and cranial-dorsal approach according to different target veins (22–24). The caudal approach or caudal-dorsal approach used in the dissection of the liver parenchyma has several limitations; for instance, it is prone to lacerate the target vein; thus, the "tenting sign of the hepatic vein" helps to identify the running of the main trunk of the hepatic vein (8), and the approach should be performed by experienced surgeons at experienced centers for well-selected

patients (23). In the cranial-ventral approach or cranial-dorsal approach, the hepatic parenchyma is transected from the root of the target hepatic vein toward its distal branches. Its primary advantage is that the liver resection plane can be clearly and safely exposed from the cranial and dorsal sides, and the branches of the target hepatic vein can then be managed separately; thus, it is regarded as a feasible and effective technique during laparoscopic hepatectomy, contributing to the process of LAH by fully exposing and protecting the hepatic veins (24, 25).

In the traditional LAMH, although the Takasaki approach was possibly used, restricted to the standing position of the surgeon, only the caudal hepatic vein-guided approach could be used when completing the right plane, meaning that the RHV would be isolation and exposure from the distal branches to the trunk, which was prone to get lost in the disconnection and lacerate the target vein, leading to massive bleeding or other serious consequences. Different from the traditional LAMH, the protocol in our study takes advantage of both the Takasaki approach and the hepatic vein-guided approach. Because squeezing liver tissue during the operation could release cancer cells, the Glissonean pedicle was implemented as a priority strategy, and ligature and transection were performed at the root of G58 and G4 first. Then, considering that the vasculature between the anterior and posterior regions of the liver varies greatly, we were not in a hurry to transect the liver parenchyma between them but instead completed the left plane of the LAMH based on the characteristics of relatively fixed and less variable nature of G4. After the disconnection of the MHV and AFV, the root of the RHV was easily exposed. Another main surgeon on the left side of the patient subsequently used a cranial approach along the ventral side of the RHV, avoiding the limitation of narrow spaces under the diaphragm when using the caudal approach, under conditions of which the RHV would be fully and safely exposed and protected. Moreover, the RHV-guided approach could effectively avoid the interference of vascular variation between the anterior and posterior regions of the liver and achieve true LAMH. No significant elevations in ALT and/or AST levels occurred on the first day after the operation, which also supported the changes after LAH.

In this study, there was still one patient relapsed at the 13th month after operation. The recurrent tumors were located both in the left lobe and the right posterior lobe of the liver. Thus, a TACE followed by target therapy and immunotherapy were performed. Fortunately, the tumors had no further progress and the patient survived with tumor in the last follow-up. Review the preoperative tumor staging of the patient, although the size of tumor is not massive, the close relationship with the G58, may be the cause of such poor prognosis.

However, this study remains subject to several limitations. First, this is a single-center study with a small sample size and no comparative sequence, which may bias the conclusion. Second, it lacks long-term follow-up to verify whether the procedure has value. Thus, this maneuver should continue to be explored.

In conclusion, counterclockwise modular LAMH using combined Glissonean pedicle (Takasaki approach) and hepatic vein-guided approaches is thought to be technically feasible for patients with a centrally located solitary HCC. The oncologic feasibility of this technique needs to be investigated based on long-term follow-up. A multicenter, large-scale, more careful study is necessary.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Ethics Committee of Binzhou Medical University Hospital, Shandong Province, China. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XC and ZZ contributed equally to this work. They are the guarantors of the manuscript and contributed to conception and design of the study, acquisition and analysis of data, and writing and revision of the manuscript. XTL, XQL, LK, and XZ contributed to pathological experiment, acquisition of the data, and writing and revision of the manuscript. BZ, WZ, QW and XL contributed to data analysis and revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Impact of sarcopenia on the future liver remnant growth after portal vein embolization and associating liver partition and portal vein ligation for staged hepatectomy in patients with liver cancer: A systematic review

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Purpose: The impact of sarcopenia on the future liver remnant (FLR) growth after portal vein occlusion, including portal vein embolization (PVE) and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has gained increasing interest. This systematic review aimed to explore whether sarcopenia was associated with insufficient FLR growth after PVE/ALPPS stage-1.

Methods: A systematic literature search was performed in PubMed, Embase, Web of Science, and Cochrane Library up to 05 July 2022. Studies evaluating the influence of sarcopenia on FLR growth after PVE/ALPPS stage-1 in patients with liver cancer were included. A predefined table was used to extract information including the study and patient characteristics, sarcopenia measurement, FLR growth, post-treatment complications and post-hepatectomy liver failure, resection rate. Research quality was evaluated by the Newcastle-Ottawa Scale.

Results: Five studies consisting of 609 patients were included in this study, with a sample size ranging from 42 to 306 (median: 90) patients. Only one study was multicenter research. The incidence of sarcopenia differed from 40% to 67% (median: 63%). Skeletal muscle index based on pretreatment computed tomography was the commonly used parameter for sarcopenia evaluation. All included studies showed that sarcopenia impaired the FLR growth after PVE/ALPPS stage-1. However, the association between sarcopenia and post-

treatment complications, post-hepatectomy liver failure, and resection rate remains unclear. All studies showed moderate-to-high quality.

Conclusions: Sarcopenia seems to be prevalent in patients undergoing PVE/ALPPS and may be a risk factor for impaired liver growth after PVE/ALPPS stage-1 according to currently limited evidence.

Systematic review registration: https://inplasy.com/, identifier INPLASY202280038.

KEYWORDS

sarcopenia, body composition, liver growth, portal vein embolization, ALPPS, liver cancer

Introduction

Liver resection remains a mainstay treatment for patients with primary or secondary liver cancer (for instance, hepatocellular carcinoma or colorectal liver metastases) with curative intent (1). However, many patients have been at an advanced stage at first diagnosis, and only 15-25% of patients are indicative of liver resection (2). For those patients who are not eligible for surgery, a majority of them are due to the limited future liver remnant (FLR), which is the remaining part of the liver after liver resection, and it serves as a key determinant for extended liver resection (3). FLR has to be sufficient to maintain normal physiologic function after liver resection, otherwise a lethal complication, post-hepatectomy liver failure will occur (4). To prevent the occurrence of liver failure after liver resection, the FLR volume limit should be > 20% of the total liver in a normal liver, > 30% in the abnormal liver (such as steatosis or post-chemotherapy), and at least 40% in the cirrhotic liver (5).

In clinical practice, many strategies have been proposed to increase the size of the FLR volume before extended liver resection. Portal vein embolization (PVE) is the commonly used technique and was first introduced by Masatoshi Makuuchi in the 1980s (6). At PVE, the branch of the portal vein leading the blood to the diseased lobes of the liver is occluded interventionally by using sponges or metal coils. By this interruption of the blood flow, the un-embolized lobes (i.e. the FLR) will be exposed to all the portal venous blood flow. This increase in flow, including exposure to nutrients, toxins, and oxygen triggers liver growth (7). Most often, after waiting for several weeks, a sufficient growth of the FLR volume has occurred and a radical liver resection can be performed safely. PVE is still the standard procedure before extended liver resection when the FLR volume is estimated to be insufficient (8). Typically, an FLR growth of 12-38% can be observed within 4-8 weeks after PVE (9). However, during the waiting period, approximately 20-40% of patients cannot proceed to hepatic resection due to insufficient liver growth or tumor progression (9, 10). Furthermore, patients with poor liver growth after PVE also have an increased risk of post-intervention complications (11).

Hepatobiliary surgeons have been committed to developing an improved method to overcome the above-mentioned limitations of PVE. In recent years, a novel strategy, called associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been proposed (12, 13). It contains two steps: in the first step, after the branch of the portal vein to the diseased lobes has been ligated (PVL, rather similar to the PVE procedure), the liver parenchyma is transected between the ligated part and the unligated part (i.e. the FLR). Once the FLR volume has increased sufficiently, liver resection can be performed to remove the liver tumor in the second step (12, 14). Interestingly, ALPPS can trigger an accelerated FLR growth in a shorter time than PVE, with a 40-80% FLR increase in only 6-9 days (12–15). However, ALPPS has high perioperative morbidity and mortality due to major surgical trauma, and the FLR growth varies among patients after ALPPS stage-1 (14). Despite surgically successful ALPPS stage-1, not all patients can complete the liver resection (14).

It is therefore of clinical importance to identify pretreatment factors that indicate a risk for insufficient FLR growth, which might allow optimizing treatment management of patients with liver cancer. Many clinical variables have been identified to be predictive for insufficient liver growth after PVE/ALPPS stage-1, for example, age, body mass index, and the diseased liver parenchyma (16). Among those, body composition is drawing increasing attention and has been assumed to be a treatable, prognostic factor in several hepatopancreatobiliary cancers after surgery (17–19). Sarcopenia is characterized by a progressive, generalized loss of skeletal muscle mass and function with aging (20). Previous studies have demonstrated sarcopenia to be associated with poor overall survival, early tumor recurrence, prolonged intensive care unit, and hospital stay after liver resection (21, 22). In recent years the influence of sarcopenia on the FLR growth after PVE/ALPPS stage-1 has been studied.

However, no research systematically summarizes the results of these studies to date. This study aimed to provide such a systematic review.

Methods and materials

The research protocol was prospectively registered at the public platform International Platform of Registered Systematic Review and Meta-analysis Protocols (https://inplasy.com/) with registration number INPLASY202280038. This study was carried out in accordance with the guidance of the Preferred Reporting Items for a Systematic Review and Meta-analysis (PRISMA) (23). The PRISMA checklist can be found in Supplementary Table S1.

Literature search and study selection

A systematic literature search was performed at four public databases: PubMed, Embase, Web of Science, and Cochrane Library and was last updated on 5 July 2022. A search strategy combining Medical Subject Headings (MeSH) terms and text words were adopted. The keywords for literature search included "sarcopenia", "body composition", "portal vein embolization", "portal vein ligation", "portal vein occlusion", "associating liver partition and portal vein ligation for staged hepatectomy". The detailed search queries are provided in Supplementary Table S2.

Records satisfying the following criteria were regarded as eligible: 1) prospective or retrospective observational studies; 2) patients with liver cancer who underwent PVE/portal vein ligation or ALPPS to induce FLR growth before liver resection; 3) FLR growth as the main outcome or one of the outcomes; 4) at least one index for sarcopenia or body composition assessment involved. Studies would be excluded if they were: 1) in the forms of narrative review, letter, reference abstract, editorial, and case report; 2) animal research.

The process of study selection was carried out by two researchers (Q.W & A.W) independently by reading the title and abstract first to screen potentially ineligible studies. After that, the full text of the screened studies was obtained to further check their eligibility in consensus. Previous reviews and the reference list of the eligible studies were also manually retrieved to detect potential eligible studies.

Data extraction and research quality evaluation

The same researchers (Q.W & A.W) independently extracted the data from the included studies and assessed the research quality. The extracted information included: study characteristics (first author, publication year, country, study design, single or multiple center studies, and sample size), patient characteristics (age, gender ratio, the procedure involved, indication, and whether also segment IV was embolized), sarcopenia related information (modality used, body composition measurement, body composition parameters, sarcopenia definition, and the incidence of sarcopenia), FLR growth (degree of hypertrophy and kinetic growth rate), independent risk factors for poor FLR growth, complications/post-hepatectomy liver failure, the liver resection rate, and the main finding of the study.

Research quality and risk of bias of the cohort or case-control studies were evaluated by using the Newcastle-Ottawa Scale tool, which is a validated and easy-to-use scale containing eight items within three domains (selection of study groups, comparability of groups, and ascertainment of exposure/outcomes) (24). The maximum score of this tool is 9, with 7-9 indicating high quality, 4-6 moderate quality, and 0-3 low quality (24). Research quality and risk of bias of the cross-sectional study were assessed by applying the Agency for Healthcare Research and Quality tool, which contains an 11-item checklist (25). The quality grades were defined as follows: 8-11 (high quality), 4-7 (moderate quality), and 0-3 (low quality). Any disagreement in data extraction and research quality appraisal between the two researchers was solved by discussion or by consulting a senior researcher (T.B.B).

Results

Study characteristics and research quality assessment

Systematic literature searching initially yielded 187 records from the four electronic databases. After the removal of ineligible studies (duplications (40), inappropriate form of research (71), animal research/case report (5), studies not related to portal vein occlusion or sarcopenia (63), and no liver growth indices available (3)), five studies remained for inclusion in this systematic review (26–30). The process of study selection is shown in Figure 1 and Supplementary Table S3.

The five studies were published between January 2020 and May 2022 and were all retrospectively designed. A total of 609 patients were evaluated, with a sample size ranging from 42 to 306 (median: 90) patients. Only one study was carried out at multiple medical centers, which were located in several European countries (29). Only one study was conducted in an Asian country (28). The Newcastle-Ottawa Scale score of the four cohort/case-control studies varied from 6 to 9 (median: 6.5) (moderate-to-high quality), while one cross-sectional study was assigned an Agency for Healthcare Research and Quality score of 6 (moderate quality) (Table 1).

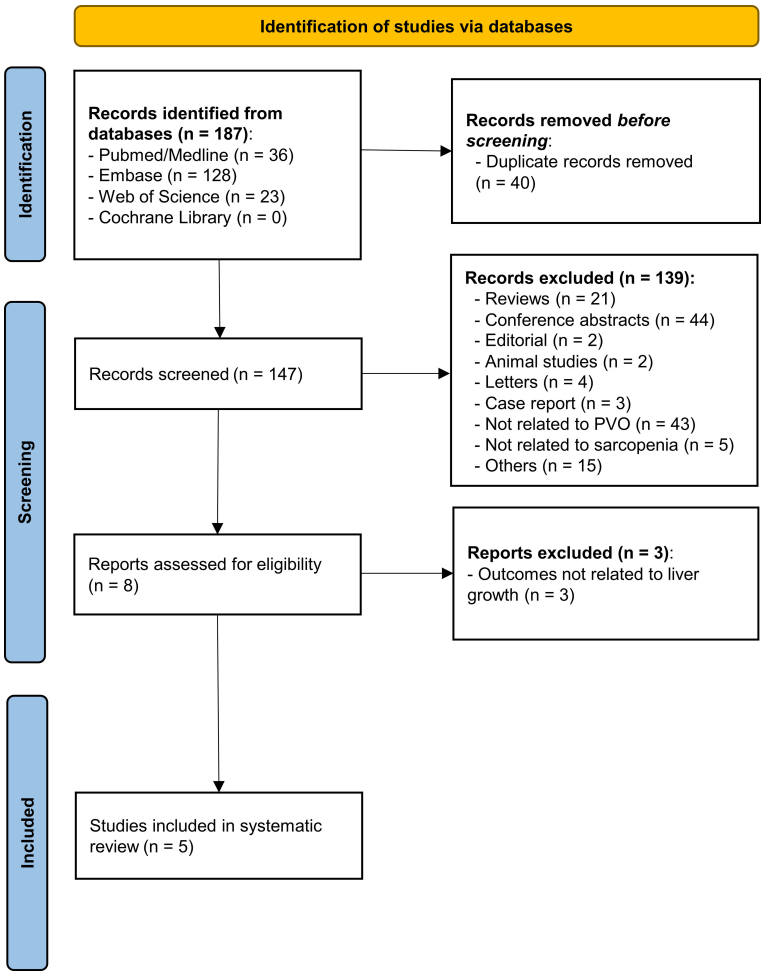

FIGURE 1
The study selection process of this study. A total of 187 records were initially identified in the four public databases. After the removal of 182 ineligible publications *via* reading the title, abstract, and full text, five studies were finally included in this systematic review. PVO, portal vein occlusion.

Patient characteristics

The average age of the included patients was between 56 and 68 years. A predominance of males was found in all studies (in total, 391/609 = 64%), which is typical of the diseases involved. Two studies exclusively focused on patients with colorectal liver metastases (26, 27), while the patients in the other three studies had varying indications. Four studies evaluated the impact of sarcopenia in patients undergoing PVE while the remaining one evaluated patients with ALPPS (30) (Table 1).

Skeletal muscle measurement and definition of sarcopenia

All body composition analyses were based on pretreatment computed tomography (CT) images: two studies stated the CT image phase used (one without contrast media and the other on images obtained in the portal venous phase) (26, 28). A slice thickness of 5 mm was reported in three studies (26, 29, 30), while slice thickness was not reported in two (27, 28). All studies measured the skeletal muscle area (at the level of the third lumber vertebra), which was converted into skeletal muscle index by being divided by squared height (m^2). Three studies adopted the skeletal muscle index to define sarcopenia (27–29). All three studies used the same threshold levels, including the one from Japan; sarcopenia was defined by a threshold of skeletal muscle index < 41 cm^2/m^2 in women, while in men two thresholds were used depending on the body mass index; at body mass index < 25 kg/m^2 a skeletal muscle index < 43 cm^2/m^2 defined sarcopenia, while the threshold was skeletal muscle index < 53 cm^2/m^2 when body mass index was > 25 kg/m^2 (27–29). The incidence of sarcopenia in the three studies ranged from 40% to 67% (median: 63%) (27–29).

TABLE 1 Study and patient characteristics.

Study ID	Publication year	Country	Study design	Single/ multiple center	Sample size	Age (years)	Gender (M/F)	Procedure	Indication	Segment IV embolization	NOS score
Schulze-Hagen[26]	2020	Germany	Retrospective, cross-sectional study	Single	42	63	32/10	PVE	CRLM	No	6†
Denbo[27]	2020	USA	Retrospective, cohort study	Single	45	58	31/14	PVE	CRLM	No	6
Yao[28]	2021	Japan	Retrospective, cohort study	Single	126	68	80/46	PVE	CCA (48%), HCC (15%), Metastatic tumor (29%), GBC (8%)	Unclear	6
Heil[29]	2021	Seven European countries	Retrospective, cohort study	Multiple	306	64/62#	183/123	PVE	CRLM (56%), HCC (7%), IHCC (12%), PHCC (15%), GBC(6%),others(4%)	37 (12%) cases	9
Reese[30]	2022	Germany	Retrospective, case-control study	Single	90	61/ 56##	65/25	ALPPS	CRLM(69%), other metastasis(11%), HCC(9%), IHCC (8%), PHCC(2%), GBC (1%)	Unclear	7

the sarcopenic vs non-sarcopenic groups; ## Low vs high kinetic liver growth groups; † scored by Agency for Healthcare Research and Quality tool; ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; CCA cholangiocarcinoma; CRLM, colorectal liver metastasis; GBC, gallbladder carcinoma; HCC, hepatocellular carcinoma; IHCC: intrahepatic cholangiocarcinoma; NOS, the Newcastle-Ottawa Scale tool; PHCC: perihilar cholangiocarcinoma; PVE, portal vein embolization.

One study applied the parameter "muscularity" to comprehensively evaluate muscle quantity and quality (28). This parameter combines skeletal muscle index and intramuscular adipose tissue content to represent both skeletal muscle quantity and quality. Another study, which was an early study with a limited sample size, did not provide their definition of sarcopenia but explored the correlation between muscle indices and liver growth (26). With a case-control design, the ALPPS study dichotomized patients using a threshold of the kinetic growth rate of 7%/week (30). The difference in skeletal muscle index between the two groups was then compared. Detailed information about sarcopenia measurement can be found in Table 2.

Liver growth rate

The degree of hypertrophy and kinetic growth rate of the FLR are two parameters commonly used for the assessment of liver growth after PVE/ALPPS stage-1. Two studies reported liver growth in the whole cohort, with a degree of hypertrophy of 8.9% and 9.5% respectively (26, 28). In three studies, the degree of hypertrophy in the sarcopenia and non-sarcopenia groups was evaluated, with a range of 8.0-8.3% and 10.8-15.2%, respectively (27–29). In the ALPPS research which dichotomized patients into low and high kinetic growth rate groups by a kinetic growth rate cutoff value of 7.0%/week, a degree of hypertrophy of 11% and 18% was observed in the two groups respectively (30) (Table 3). Compared with a kinetic growth rate of 2.6-4.0%/week in the non-sarcopenia group, the sarcopenia group demonstrated a significantly lower kinetic growth rate of 2.0%/week in two studies (27, 29). One study reported an overall kinetic growth rate of 3.6%/week for the whole study cohort (26).

In the three studies that performed multivariable logistic regression analysis, all identified sarcopenia as an independent factor for poor FLR growth (28–30). The other independent variables detected were initial FLR volume, total bilirubin level, and body mass index. All studies concluded that sarcopenia was associated with poor FLR growth after PVE/ALPPS stage-1 (Table 3).

Post-treatment complications, post-hepatectomy liver failure, and resection rate

Two studies reported complications after PVE intervention, with a major complication (≥ III Clavien-Dindo classification) of 52% and 31% in the sarcopenia group versus 41% and 33% in the non-sarcopenia group respectively (both statistically non-significant) (28, 29). The incidence of post-hepatectomy liver failure was reported in two PVE studies and one ALPPS study. An opposite result was observed in the two PVE studies where the incidence of postoperative liver failure was 38% and 16% in the sarcopenia group versus 17% and 22% in the non-sarcopenia group respectively (one significant while the other not) (28, 29). The ALPPS study reported an incidence of post-hepatectomy liver failure of 20% and 7% after ALPPS stage-1 in the low and

TABLE 2 Body composition measurement and sarcopenia definition.

Study ID	Modality for body composition measurement	Body composition measurement	Muscle quantity Parameter(s)	Muscle quality parameter	Other parameter(s)	Sarcopenia definition	Sarcopenia cases (incidence)
Schulze-Hagen [26]	5 mm slice, portal venous CT images	Skeletal muscle area at L3 (SMI, SMA); the largest psoas muscle diameter (PMCS); automatic machine learning algorithm (PMV)	PMV, PMCS, SMI, SMA	No	NA	NA	NA
Denbo [27]	CT images	Skeletal muscle area, visceral adipose area, and subcutaneous adipose area at L3	SMI	No	VAI, SAI	SMI < 41 cm^2/m^2 (women); SMI < 43 cm^2/m^2 (men with BMI of < 25 kg/m^2), and < 53 cm^2/m^2 (men with BMI > 25 kg/m^2)	18 (40%)
Yao[28]	Plain CT images	Skeletal muscle area, visceral adipose area, and subcutaneous adipose area at L3	SMI	IMAC	Visceral-to-subcutaneous adipose tissue area ratio	SMI: 41 cm^2/m^2 (women); 43 cm^2/m^2(men with BMI < 25 kg/m^2), and 53 cm^2/m^2 (men with BMI > 25 kg/m^2). IMAC: - 0.229 (women) and - 0.358 (men).	85 (67%)
Heil[29]	5 mm slice CT images	Skeletal muscle area, visceral adipose area, and subcutaneous adipose area at L3	SMA, SMI	No	Subcutaneous adipose area, Visceral adipose area, SAI, VAI	SMI < 41 cm^2/m^2 (women); SMI < 43 cm^2/m^2 (men with BMI of < 25 kg/m^2), and < 53 cm^2/m^2 (men with BMI > 25 kg/m^2)	194 (63%)
Reese [30]	5 mm slice CT images	Area of the psoas major muscles at L3	SMI	NA	NA	NA	NA

BMI, body mass index; CT, computed tomography; IMAC, intramuscular adipose tissue content; L3, the 3rd lumbar vertebra; NA, not available/applicable; PMV, psoas muscle volume; PMCS, psoas muscle cross-sectional area; SAI, subcutaneous adipose index; SMA, skeletal muscle area; SMI, skeletal muscle index; VAI, Visceral adipose index.

high kinetic growth rate groups respectively, but also here the difference was not statistically significant (30). There was a significant difference of the post-hepatectomy liver failure incidence between the low and high kinetic growth rate groups after ALPPS stage-2 (i.e. liver resection) with an incidence of 31% and 7%, respectively ($p < 0.05$) (30).

Overall resection rate was reported to be 83% and 73% respectively in two of the PVE studies (28, 29) and 87% in the ALPPS study (30). One study reported a significantly lower resection rate after PVE in the sarcopenia group, compared with the non-sarcopenia group (66% vs 87%) (29). Interestingly, as a study evaluated factors that might affect liver growth after PVE, one study excluded patients with insufficient FLR growth after PVE and only included patients who proceed to liver resection (28). In that study, 26 patients did not undergo liver resection. In the ALPPS study, the resection rate was 84% in the low kinetic growth rate group, but that was not statistically significantly less than the 93% resection rate in the high kinetic growth rate group (30). Detailed information can be found in Table 3.

Discussion

The present study systematically reviews the association between skeletal muscle loss and FLR growth after PVE/ALPPS stage-1. A high incidence of sarcopenia among patients undergoing PVE was observed, and sarcopenia was associated with impaired FLR growth after PVE/ALPPS stage-1. However, its relationship with post-treatment complication rate, post-hepatectomy liver failure as well as surgical resection rate remains unclear.

The median incidence of sarcopenia among patients undergoing PVE in the included studies was 63%, which was higher than the reported incidence in patients with colorectal liver metastases (17-26%) (18, 31) or hepatocellular carcinoma (30-54%) (18), the two most common indications for PVE/ALPPS. Generally, the incidence of sarcopenia in patients with cancer has a wide variation due to different tumor types, tumor stages, measuring methods, and indices and criteria used (32). In the case of PVE/ALPPS, the indications usually vary among centers, which may also contribute to a varying and higher incidence of sarcopenia. Another explanation for the high observed incidence of sarcopenia is that the patients requiring PVE/ALPPS often have a chronically diseased liver such as liver cirrhosis (33) or have experienced several cycles of chemotherapy (e.g. neoadjuvant chemotherapy in patients with colorectal liver metastases) (31, 34). Considering that patients undergoing PVE/ALPPS experience two major interventions in a relatively short time, the patients may be at a high risk of malnutrition if additional calories and protein cannot be

TABLE 3 Future liver remnant growth, post-treatment complication rate and post-hepatectomy liver failure.

Study ID	Degree of hypertrophy of FLR	KGR of FLR	Independentrisk factorsfor poor liver growth	Complication rate/PHLF incidence	Surgical resection rate	Main findings
Schulze-Hagen [26]	8.9% (overall)	3.6%/ week (overall)	NA	NA	NA	Psoas muscle volume and PMCS positively correlates with KGR of FLR after PVE
Denbo [27]	8.3% vs 15.2%*	2.0 vs 4.0%/ week*	NA	NA	NA	Sarcopenia and related body composition indices are strongly associated with impaired liver growth after PVE
Yao[28]	9.5% (overall) 8.2% vs 10.8%*	NA	Initial FLR, total bilirubin, muscularity/IMAC#	52% vs 41% (N.S) for major complication##; 38% vs 17%* for PHLF grade B	83% (overall)	Low muscularity leads to poor liver hypertrophy after PVE and is also a predictor of PHLF
Heil[29]	8% vs 11%*	2.0 vs 2.6%/ week*	Sarcopenia, initial FLR	31% vs 33% (N.S) for major complication; 16% vs 22% (N.S) for PHLF	73% (overall); 66% vs 87% *	Sarcopenia is associated with reduced KGR and resectability in patients undergoing PVE
Reese [30]	11% vs 18%†	Cut-off value: 7%/ week	Body mass index, skeletal muscle index	20% vs 7% (N.S) for PHLF after ALPPS stage-1; 31% vs 7%* for PHLF after ALPPS stage-2†	87% (overall); 84% vs 93% (N.S)†	Low sarcopenia muscle index and a high body mass index correlate with impaired liver regeneration and increased liver dysfunction after ALPPS

Data comparison is presented as the **sarcopenia** versus **non-sarcopenia** groups, unless otherwise specified. * statistically significant; # according to two multivariable logistic regression models; ## by the Clavien–Dindo grading system; † low vs high KGR groups according to a cutoff value of 7%/week. ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; FLR, future liver remnant; IMAC, intramuscular adipose tissue content; KGR, kinetic growth rate; PHLF, post-hepatectomy liver failure; PMCS, psoas muscle cross-sectional area; PVE, portal vein embolization; NA, not available/applicable; N.S, not significant.

supplemented in time. These additional clinical conditions may further impair patients' nutritional status. The higher incidence of sarcopenia also implies that the evaluation of body composition in these patients should be paid more attention to the perioperative assessment.

All included studies applied CT-based measurement for muscle mass assessment. This is reasonable given that CT is a commonly used imaging modality for the diagnosis and staging of patients with liver cancer. Furthermore, in the setting of PVE/ALPPS, CT is also widely applied for liver volumetry in pretreatment evaluation and to evaluate liver volume change after intervention. That is to say, the evaluation of body composition does not pose an extra burden for these patients. Dual-energy X-ray absorptiometry and bioelectrical impedance analysis are the other two commonly used methods for body composition measurement (35), but, to the best of our knowledge, they have not been employed in predicting liver remnant growth after surgery.

However, when analyzing the body composition, only limited details on CT imaging were provided in the included studies. Only two studies reported the imaging phase and just three studies described the slice thickness. It has been shown that these factors exert a considerable impact on the results of body composition analysis (36). In a study by Morsbach et al, the influence of contrast media and slice thickness on CT body composition segmentation was evaluated (37). They found that the skeletal muscle mass area, adipose tissue area, and muscle and fat attenuation (expressed in Hounsfield Units) showed a significant change after contrast media administration. There also was a significant effect on the area measurements (skeletal muscle mass area and adipose tissue area) when the slice thicknesses were adjusted. A systematic review summarized a group of CT-related factors which may affect the sarcopenia assessment (38). The CT parameters that according to the review can potentially affect the assessment included the use of contrast media, kilovoltage, CT manufacture and model, patient position, and slice thickness (38). Considering such many potential confounders, researchers need to bear them in mind when measuring body composition before transferring their results into clinical implementation. Besides, to make the findings reproducible and to increase the comparability among different studies, it also seems necessary to provide such information when reporting the body composition results.

Recent research has identified muscle quality, which can be determined by the infiltration of fat into muscle, as an independent prognostic factor in several types of cancer (39–41). In the present review, only one study adopted a composite index that combined skeletal muscle quantity and quality (named "muscularity") (28), while the others only assessed skeletal muscle quantity. Theoretically, muscularity should have a better performance in the prediction of the clinical outcomes, including the FLR growth after PVE/ALPPS stage-1, but this needs to be confirmed by further research. Besides, as highlighted by the European Working Group on Sarcopenia in Older People 2 evaluation of muscle strength and physical performance is equivalent to the evaluation of muscle quantity and quality in the diagnosis of sarcopenia (20). Future research assessing the impact of sarcopenia on liver growth and the

clinical outcomes in patients with cancer can also consider taking these components into account.

Even though an obvious heterogeneity was displayed in the included studies, all of them drew a similar conclusion that sarcopenia had a negative influence on liver growth after PVE/ALPPS stage-1. Furthermore, sarcopenia seemed to have an association with a higher risk of post-hepatectomy liver failure and lower surgical resection rate in the patient who underwent PVE/ALPPS, although the results were inconsistent in this review. Sarcopenia is also a risk factor for poor overall survival in patients with liver cancer (21). But the impact of sarcopenia on the overall survival of patients who undergo PVE/ALPPS remains unknown.

Tumor progression is another common reason for patients not being able to reach curative surgery after PVE. Its incidence is even greater than that of insufficient liver growth contributing to a "failed" PVE, 19% vs 11%, as reported in the international DRAGON trial (42). This may be partly due to the slow growth after PVE, approximately 4-8 weeks to induce an FLR growth of 12-38% (9, 43). During this long waiting interval, the tumor is likely to progress, leaving the patient not eligible for surgery anymore. Until now, only one study explored the influence of sarcopenia on the resectability in patients undergoing PVE. It showed that sarcopenia (defined as psoas muscle index < 500 mm^2/m^2) was a risk factor for unresectability (44). However, the sample size of that research was limited (only 88 patients). On the other hand, a meta-analysis that included 13 studies revealed that sarcopenia was also significantly associated with tumor recurrence (adjusted hazard ratio: 1.76) (21). Whether sarcopenia results in both impaired liver growth and increased tumor progression after PVE, and whether improvement of patient sarcopenia status can increase resectability and long-term prognosis are still unclear.

Even though all studies claimed that sarcopenia impaired liver growth, it is of note to point out that sarcopenia should only be considered as a cofactor that undermines FLR growth after PVE/ALPPS stage-1. To put it another way, other vital clinical variables also determine liver growth after PVE/ALPPS stage-1. Three of the included studies also detected initial FLR volume, total bilirubin level, and body mass index as independent risk factors for insufficient liver growth (28–30). As a prognostic factor, the initial FLR volume was also reported in previous studies (45–47). Other reported indicators include age (45, 48), embolic agent (49–51), segment IV embolization (52, 53), chemotherapy (45), and portal collaterals (54, 55). It is assumed that a combination of these risk factors may improve the predictive accuracy for the FLR growth after PVE/ALPPS stage-1.

There are some limitations in this study. This review was first limited by the small number of included studies, all with a limited sample size (median: 90). Also, there were no prospective studies and only one multicenter study. The lack of large prospective multicenter studies may undermine a convincing conclusion drawn from this systematic review. Second, due to the limited study number and methodological heterogeneity, it was not possible to perform a meta-analysis and synthesize the results to provide a pooled relative risk value of sarcopenia for poor FLR growth. Third, the limited number of studies and the research heterogeneity also made it difficult to identify the most accurate and reliable parameter for sarcopenia assessment, given that a variety of indices were used for muscle mass evaluation. As summarized in a review, as many as 14 methods are currently available for sarcopenia assessment (32). Nevertheless, an index combining skeletal muscle quantity and quality evaluation (for example, muscularity) seems more rational and effective. Future studies can be designed to compare these indices. Lastly, there seems to be a need to improve the research and reporting quality of studies on sarcopenia. For example, detailed information on CT imaging during body composition measurement is required to ensure a reproducible and reliable study.

Conclusions

Research on the impact of sarcopenia on liver growth after PVE/ALPPS stage-1 is still in its initial stage. Based on currently available evidence, sarcopenia seems to have a high incidence in patients undergoing PVE/ALPPS and it may impair FLR growth. Its relationship with post-treatment complications, post-hepatectomy liver failure, and resection rate requires further comprehensive research.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author/s.

Author contributions

Conceptualization, QW, and ZL. Methodology, QW and AW. Validation, AW, ZL, and TB. Formal analysis, QW, AW and ZL. Investigation, ZL. Data curation, AW, and ES; writing—original draft preparation, QW, and AW. Writing—review and editing, ES and TB. Visualization, QW. Supervision, ZL, and TB. Project administration, QW. Funding acquisition, QW.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Assessment of the prognostic value of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in perihilar cholangiocarcinoma patients following curative resection: *A multicenter study of 333 patients*

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Background & Aims: Tumor-associated chronic inflammation has been determined to play a crucial role in tumor progression, angiogenesis and immunosuppression. The objective of this study was to assess the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in perihilar cholangiocarcinoma (pCCA) patients following curative resection.

Methods: Consecutive pCCA patients following curative resection at 3 Chinese hospitals between 2014 and 2018 were included. The NLR was defined as the ratio of neutrophil count to lymphocyte count. PLR was defined as the ratio of platelet count to lymphocyte count. The optimal cutoff values of preoperative NLR and PLR were determined according to receiver operating characteristic (ROC) curves for the prediction of 1-year overall survival (OS), and all patients were divided into high- and low-risk groups. Kaplan-Meier curves and Cox regression models were used to investigate the relationship between values of NLR and PLR and values of OS and recurrence-free survival (RFS) in pCCA patients. The usefulness of NLR and PLR in predicting OS and RFS was evaluated by time-dependent ROC curves.

Results: A total of 333 patients were included. According to the ROC curve for the prediction of 1-year OS, the optimal cutoff values of preoperative NLR and PLR were 1.68 and 113.1, respectively, and all patients were divided into high- and low-risk groups. The 5-year survival rates in the low-NLR (<1.68) and low-PLR groups (<113.1) were 30.1% and 29.4%, respectively, which were significantly higher than the rates of 14.9% and 3.3% in the high-NLR group (≥1.68) and high-PLR group (≥113.1), respectively. In multivariate analysis, high NLR and high PLR were independently associated with poor OS and RFS for pCCA patients. The time-dependent ROC curve revealed that both NLR and PLR were ideally useful in predicting OS and RFS for pCCA patients.

Conclusions: This study found that both NLR and PLR could be used to effectively predict long-term survival in patients with pCCA who underwent curative resection.

KEYWORDS

neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, perihilar cholangiocarcinoma, hepatectomy, survical

Introduction

Perihilar cholangiocarcinoma (pCCA) is a rare tumor that accounts for 50-70% of all biliary tract tumors and tends to occur at the site of biliary fusion or in the right or left liver duct (1, 2). Curative resection was the only treatment for achieving a potential cure, but long-term survival was poor (5-year survival ranged from 25% to 40%) (1, 3, 4). Accurate prediction of prognosis can better help surgeons develop personalized treatment strategies. However, the current prediction methods only include tumor markers and pathological tests. Assessment methods with more dimensions may enable more accurate prediction of patient prognosis.

Studies have shown that the tumor microenvironment and tumor-associated chronic inflammation play a crucial role in tumor progression (5, 6). During the development of pCCA, changes in inflammation levels further lead to immunosuppression and metabolic reprogramming and ultimately promote tumor progression. The condition of these patients could be reflected by complete blood count (CBC) markers (7), such as neutrophils, platelets, and lymphocytes. Specifically, neutrophils can directly promote tumor progression, metastasis and angiogenesis by releasing some enzymes (8–10). Platelets protect circulating tumor cells by encapsulating them in blood clots, protecting them from being lysed by natural killer cells or releasing thrombin to promote tumor proliferation and growth (11–13). Lymphocytes realize the tumor immune response through the recognition, killing and clearance of tumor cells, thereby playing a role in immunosuppression and antitumor immunity (14). Many studies have now confirmed that the inflammatory markers neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) (15–17) are associated with the prognosis of many cancers, such as hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, gallbladder carcinoma, and pancreatic cancer (18–22). However, the relationship between values of NLR and PLR and pCCA prognosis has not been studied.

The objective of this study was to assess the prognostic value of NLR and PLR in pCCA patients following curative resection. This was the first study conducted with data from a multicenter database on the long-term prognosis of NLR and PLR in pCCA patients undergoing curative resection.

Abbreviations: AJCC, American Joint Committee on Cancer; ALB, albumin; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate transaminase; CA 19-9, carbohydrate antigen 19-9; CBC, complete blood count; CEA, carcinoembryonic antigen; CI, confidence interval; CTC, circulating cancer cells; HR, hazard ratio; INR, international normalized ratio; NLR, neutrophil-to-lymphocyte ratio; pCCA, perihilar cholangiocarcinoma; OR, odds ratio; OS, overall survival; PLR, platelet-to-lymphocyte ratio; RFS, recurrence free survival; ROC, receiver operating characteristic; TB, total bilirubin.

Methods

Patient selection

Patients diagnosed with pCCA following curative resection between 2014 and 2018 at three hospitals in China (Southwest Hospital, Sichuan Provincial People's Hospital, and Affiliated

Hospital of Qinghai University) were included. The diagnosis of pCCA was confirmed by postoperative pathology. Patients who died within 30 days after surgery, those who had other autoimmune diseases, those who had inflammatory disease, or those whose data were missing important variables were excluded. Curative resection for this purpose included partial hepatic resection, cholangiotomy, biliary anastomosis, and lymph node dissection. If the tumor invaded the hepatic vein or hepatic artery, lateral vascular reconstruction was performed. Curative resection was defined as the resection of tissue with margins that were clear under the microscope without visible tumor cells. The study was approved by the Institutional Review Board of the Southwest Hospital of Chongqing, China (No. KY2021129). Because the study was retrospective and all data were anonymized, informed consent was not needed.

Clinicopathological variables

The demographic variables included age, sex, American Society of Anesthesiologists (ASA) grade, preoperative jaundice, cirrhosis, chronic hepatitis, and hepatolithiasis. The laboratory variables included alanine aminotransferase (ALT), aspartate transaminase (AST), carbohydrate antigen 19-9 (CA19-9), total bilirubin (TB) and preoperative neutrophils, platelets and lymphocytes. The pathological variables included cirrhosis, maximum tumor size, nerve invasion, the 8th American Joint Committee on Cancer (AJCC) stage (23), the Bismuth classification (24), tumor differentiation, macro- or microvascular invasion, lymph node metastasis, and peripheral nerve invasion. Both portal vein invasion and hepatic artery invasion were considered macrovascular invasion. The operative variables included the extent of hepatectomy (major *vs*. minor), intraoperative blood loss, and perioperative blood transfusion.

For laboratory parameters, patients were divided into normal and abnormal groups using the upper or lower limit of the normal values used in clinical practice, such as 35 g/L for albumin, 40 U/L for AST, 40 U/L for ALT, 1 mg/dL TB, and 1.15 for INR, as reported in a previous study (25–28). Cirrhosis was confirmed by histopathological examination. Major hepatectomy was defined as the resection of three or more segments of the Couinaud liver, and minor hepatectomy was defined as the resection of fewer than three segments (29). Preoperative jaundice was defined as a preoperative total bilirubin higher than 34 μmol/L.

Patient follow-up

Patients were followed-up after curative resection regularly. The postoperative surveillance strategy involved physical examination, abdominal ultrasonography and laboratory control every 2 months in the first and second years after resection, then once every three months from the third to the fifth year and finally once every six months. At each visit, tumor markers such as carcinoembryonic antigen (CEA) and CA19-9 were included, and computed tomography and/or magnetic resonance cholangiopancreatography examinations were also performed. Overall survival (OS) was computed as the interval between the date of surgery and the date of death or the last follow-up. The recurrence-free survival (RFS) was computed as interval from the day of resection to the day of diagnosis of tumor recurrence for recurrent patients or from the day of resection to the day of death or date of last follow-up for patients without recurrence.

Statistical analysis

Continuous variables conforming to a normal distribution were expressed as the mean ± standard deviation and analyzed using *t tests*; those conforming to nonnormal distributions were expressed as the median (quartile) and tested with the Mann–Whitney U test. Categorical variables were expressed as numbers and percentages and compared between groups using the $\chi 2$ test or Fisher's exact test. According to the ROC curve for the prediction of 1-year OS, the optimal cutoff values of preoperative NLR and PLR were calculated, and all patients were divided into high- and low-risk groups. RFS and OS were evaluated using the Kaplan–Meier method, and the differences between the two groups were examined by the log-rank test. Those variables with significance at $P < 0.1$ confirmed as noncollinearity by a variance inflation factor < 3 were entered into multivariable Cox proportional hazard models after univariable analyses, and 95% CI and hazard ratio values were calculated. The ability of NLR and PLR to predict OS and RFS was evaluated by time-dependent ROC curves. All data analyses were performed using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA) and R software (version 3.5.1. http://www.r-project.org/). All P values reported were two-sided, and a P value < 0.05 was considered statistically significant.

Results

Clinicopathologic and operative variables of patients

Among the 404 patients who underwent curative resection for pCCA between January 2014 and January 2018, we excluded 24 patients who had recurrent pCCA, 18 patients for whom information was missing, 26 patients with incomplete treatment, and 4 patients who had other autoimmune diseases as shown in Figure 1. Thus, 333 pCCA patients were included in the final analytic cohort (213 male and 120 female patients), and the mean age was 57.03 ± 9.94 years.

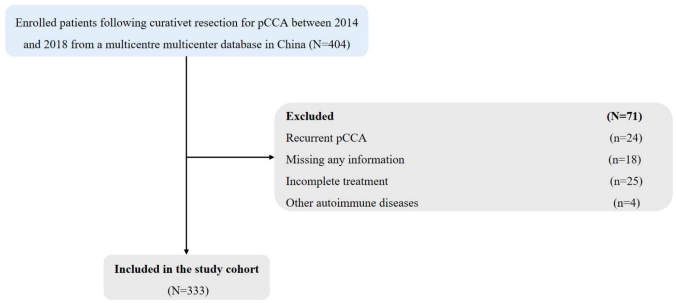

FIGURE 1
Flow chart of patient inclusion. pCCA, perihilar cholangiocarcinoma.

ROC curves and cutoff values and groupings of NLR and PLR

According to the ROC curve, as shown in Figure 2, the optimal cutoff values of preoperative NLR and PLR for predicting 1-year OS were calculated to be 1.68 and 113.1, respectively. The ROC areas under the curve for NLR and PLR were 0.729 (95% CI: 0.663-0.795) and 0.786 (95% CI: 0.724-0.849), respectively. And according to their cutoff values, NLR < 1.68 was defined as low NLR (n = 155, 46.5%), NLR ≥ 1.68 was defined as high NLR (n =178, 53.5%), PLR < 113.1 (n = 231, 69.4%) was defined as low PLR, and PLR ≥ 113.1 was defined as high PLR (n = 102, 30.6%). The comparisons of patients' clinicopathologic and operative variables between those with high and low NLR and PLR are shown in Table 1. High CA 19-9 level, poor differentiation and microvascular invasion were more commonly seen in high NLR patients ($P < 0.05$). Cirrhosis and lymph node metastasis were more commonly seen in high PLR patients ($P < 0.05$).

Survival outcome

The median period of follow-up times, 5-year OS rates and 5-year RFS rates for all pCCA patients were 21.0 (12.0, 36.0) months, 22.0% and 10.5%, respectively. Regarding NLR, 5-year OS rates and 5-year RFS rates occurred for 14.9% and 5.2% in high NLR patients, respectively, and for 30.1% and 16.1% in low NLR patients, respectively. The rates of death and recurrence in high NLR patients were significantly lower in low NLR patients, as shown in Table 2 (death, $P = 0.004$; recurrence, $P = 0.084$). Regarding PLR, 5-year OS rates and 5-year RFS rates occurred for 3.3% and 5.0% in high PLR patients, respectively, and for 29.4% and 13.3% in low PLR patients, respectively. The rates of death and recurrence in high PLR patients were significantly lower in low PLR patients, as shown in Table 2 (death, $P = 0.001$; recurrence, $P = 0.031$). The survival and recurrence curves of high/low NLR patients and high/low PLR patients are shown in Figure 3.

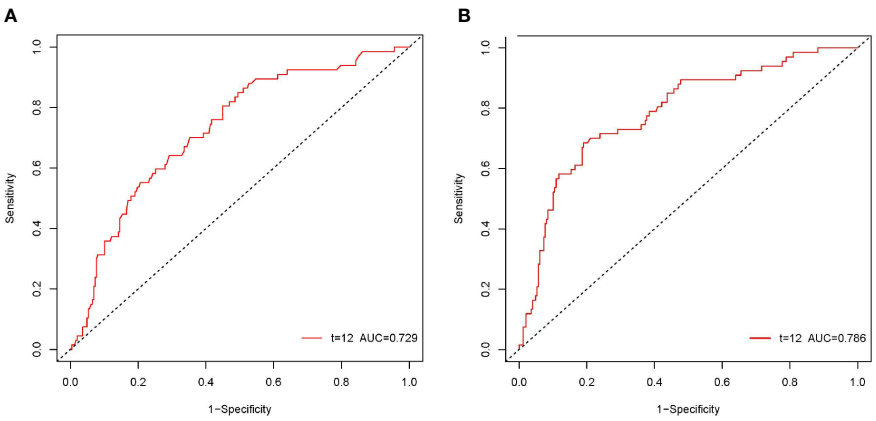

FIGURE 2
The ROC curves of the NLR and PLR in patients with pCCA. The ROC area of NLR was 0.729 **(A)**. The ROC area of PLR was 0.786 **(B)**.

TABLE 1 Baseline for pCCA patients categorized by NLR, PLR and their clinical pathological characteristics.

Variables	NLR			PLR		
	< 1.68 (n = 155)	≥ 1.68 (n = 178)	*P* value	< 113.1 (n = 231)	≥113.1 (n = 102)	*P* value
Age, years*	56.89 ± 10.73	57.15 ± 9.22	0.815	56.51 ± 10.19	58.20 ± 9.29	0.154
Gender, male	101 (65.16)	112 (62.9)	0.671	149 (64.5)	64 (62.7)	0.758
ASA score > 2	12 (7.7)	22 (12.4)	0.165	26 (11.6)	8 (7.8)	0.343
Comorbidity	40 (25.8)	41 (23.0)	0.556	60 9 (26.0)	21 (20.6)	0.291
Preoperative jaundice	118 (76.1)	142 (79.8)	0.442	179 (77.5)	81 (79.4)	0.696
ALB (g/L)*	36.27 ± 4.71	37.25 ± 4.23	0.045	36.71 ± 4.70	37.00 ± 3.94	0.593
ALT (U/L)*	71.00 (45.50, 157.00)	83.50 (52.00, 169.00)	0.927	73.70 (46.00, 162.00)	81.15 (52.28, 161.00)	0.726
AST (U/L)*	74.00 (45.00, 136.00)	83.00 (52.75, 138.00)	0.735	75.40 (49.70, 130.00)	85.50 (49.95, 134.00)	0.665
Hb (g/L)	121.23 ± 25.51	122.75 ± 23.84	0.576	122.88 ± 27.76	120.15 ± 15.20	0.352
TB (mg/dL)*	150.40 (25.70, 279.40)	145.30 (51.95, 248.05)	0.557	150.40 (46.40, 263.90)	138.70 (32.40, 263.10)	0.839
CA 19-9 (U/L)*	121.00(34.20, 277.17)	140.07 (60.00, 364.65)	0.024	127.38 (42.53, 308.80)	134.52 (61.73, 400.00)	0.200
INR*	0.97 ± 0.10	0.97 ± 0.10	0.562	0.96 ± 0.10	0.98 ± 0.11	0.105
NLR	1.11 ± 0.32	3.15 ± 1.45	<0.001	1.76 ± 1.06	3.18 ± 1.81	<0.001
PLR	55.00 (38.92, 81.94)	107.27 (68.53, 144.45)	<0.001	60.00 (42.97, 81.25)	144.68 (126.88, 185.31)	<0.001
Cirrhosis	15 (9.7)	14 (7.8)	0.559	25 (10.8)	4 (3.9)	0.04
Chronic hepatitis	13 (9.0)	14 (7.8)	0.862	18 (7,8)	9 (8.8)	0.751
Hepatolithiasis	14 (8.3)	10 (5.6)	0.229	20 (8.7)	4 (3.9)	0.123
Maximum tumor size (cm)*	2.84 ± 1.24	3.05 ± 1.39	0.137	2.91 ± 1.26	3.05 ± 1.47	0.370
Poor differentiation	15 (9.7)	34 (19.1)	0.015	31 (13.4)	18 (17.6)	0.316
Macrovascular invasion	34 (21.9)	53 (29.8)	0.104	54 (23.4)	33 (32.4)	0.086
Microvascular invasion	11 (7.1)	26 (14.6)	0.030	23 (10.0)	14 (13.7)	0.313
8th AJCC stage III-IV	80 (51.6)	89 (50.0)	0.769	114 (49.4)	55 (53.9)	0.442
Bismuth classification III-IV	121 (78.1)	134 (75.3)	0.550	183 (79.2)	72 (70.6)	0.086
Lymph node metastasis	48 (30.1)	62 (34.8)	0.455	67 (29.0)	43 (42.1)	0.019
Peripheral nerve invasion	50 (32.3)	51 (28.7)	0.475	75 (32.5)	26 (25.5)	0.202
Intraoperative blood loss (ml)	700.0 (400.0, 1000.0)	700.0 (437.5, 1000.0)	0.137	700.0 (400.0, 1000.0)	700.0 (500.0, 1400.0)	0.116
Major hepatectomy	114 (73.5)	128 (71.9)	0.738	169 (73.2)	73 (71.6)	0.764

*Values are the mean ± standard deviation or median and quartile.
AJCC, American Joint Committee on Cancer; ALB, albumin level; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate transaminase; CA 19-9, carbohydrate antigen 19-9; INR, international normalized ratio; NLR, neutrophil-to-lymphocyte ratio; pCCA, perihilar cholangiocarcinoma; PLT, platelets level; PLR, platelet-to-lymphocyte ratio; TB, total bilirubin.

NLR and PLR as prognostic markers

On multivariable Cox regression analyses, six variables were independently associated with OS in pCCA patients as shown in Table 3, including NLR < 1.68 *vs.* ≥ 1.68) (HR: 1.417, 95% CI: 1.071-1.875, P=); PLR (< 113.1 *vs.* ≥ 113.1) (HR: 2.223, 95% CI: 1.671-2.957); CA 19-9 (> 150 *vs.* ≤ 150 U/L) (HR: 1.610, 95% CI: 1.144-2.266); maximum tumor size (< 3 cm *vs.* ≥ 3 cm) (HR: 1.576, 95% CI: 1.204-2.062); macrovascular invasion (Yes *vs.* No) (HR: 1.416, 95% CI: 1.055-1.902); and lymph node metastasis (Yes *vs.* No) (HR: 2.012, 95% CI: 1.531-2.644). There were five independent variables associated with RFS in pCCA patients as shown in Table 4, including NLR (< 1.68 *vs.* ≥ 1.68) (HR: 1.598, 95% CI: 1.224-2.088); PLR (< 113.1 *vs.* ≥ 113.1) (HR: 2.138, 95% CI: 1.613-2.833), maximum tumor size (< 3 cm *vs.* ≥ 3 cm) (HR: 1.398, 95% CI: 1.080-1.812); macrovascular

TABLE 2 Comparisons of survival outcomes between pCCA patients with high and low NLRs and PLRs.

Survival outcomes	Total (n = 333)	NLR			PLR		
		< 1.68 (n = 155)	≥ 1.68 (n = 178)	*P* value	< 113.1 (n = 231)	≥ 113.1 (n = 102)	*P* value
Period of follow-up, months*	21.0 (12.0, 36.0)	27.0 (16.0, 49.0)	16.5 (8.8, 30.0)	<0.001	26.0 (15.0, 45.0)	12.0 (6.0, 22.3)	<0.001
Death during the follow-up	234 (70.3%)	97 (62.6%)	137 (77.0%)	0.004	146 (63.2%)	88 (86.3%)	0.001
Recurrence during the follow-up	267 (80.1%)	118 (76.1%)	149 (83.7%)	0.084	178 (77.1%)	89 (87.3%)	0.031
OS, months*	33.9 (30.8-37.2)	42.2 (37.4-46.9)	26.7 (22.6-30.8)	<0.001	40.7 (36.8-44.6)	17.8 (14.1-21.5)	<0.001
1-yr OS rate, %	76.1	88.3	65.4		87.4	50.3	
3-yr OS rate, %	33.7	47.1	21.4		44.3	8.7	
5-yr OS rate, %	22.0	30.1	14.9		29.4	3.3	
RFS, months	28.2 (25.5-30.9)	35.5 (31.4-39.6)	21.6 (18.4-24.7)	<0.001	33.9 (30.6-37.0)	15.0 (11.4-18.6)	<0.001
1-yr RFS rate, %	64.0	76.7	52.9		75.2	38.3	
3-yr RFS rate, %	33.9	47.4	21.5		43.8	10.1	
5-yr RFS rate, %	10.5	16.1	5.2		13.3	5.0	

*Values are the mean ± standard deviation or median and quartile.
OS, overall survival; RFS, recurrence-free survival; INR, international normalized ratio; NLR, neutrophil-to-lymphocyte ratio; pCCA, perihilar cholangiocarcinoma; PLR, platelet-to-lymphocyte ratio.

invasion (yes *vs*. no) (HR: 1.367, 95% CI: 1.030-1.815); and lymph node metastasis (yes *vs*. no) (HR: 1.638, 95% CI: 1.652-2.776). Moreover, NLR and PLR were found to be useful in effectively predicting OS and RFS through the result of the time-dependent ROC analysis, as shown in Figure 4.

Discussion

Cholangiocarcinoma represent a class of malignant tumors that originate in epithelial cells, of which hilar cholangiocarcinoma is the most common type, occurring at the site of biliary fusion or in the right or left liver duct (30) and accounting for approximately 50% of all cases. Resection is the only treatment with a potential of curing it. However, even after curative resection, the 5-year survival rate of patients is only 20% to 40% (1–3). Therefore, it is of great significance to actively identify prognostic factors that affect the long-term prognosis of pCCA. Many studies have demonstrated that chronic inflammation is associated with the occurrence and progression of tumors (5, 31). Studies have shown that cancer originates from chronic inflammatory sites, and there are a large number of inflammatory cells in tumor biopsies. Chronic inflammation provides a preferred microenvironment for the occurrence, progression and metastasis of tumors (5). During chronic inflammation, inflammatory cells and cytokines may act as tumor promoters, promoting cell survival, proliferation, invasion, and angiogenesis (5). Specific markers in the CBC panel of tests can be used as an accurate reflection of patients' inflammatory levels, *via* generation of parameters such as NLR and PLR, and, thus, potentially assist clinicians in better predicting long-term prognosis in pCCA patients.

In previous studies, NLR and PLR have been shown to be important markers of long-term prognosis in patients with other digestive system tumors (18, 22). Hsiang et al. analyzed the long-term prognosis of 239 patients with hepatocellular carcinoma who underwent curative resection and found that the median OS of patients with NLR < 2.4 was significantly better than the median OS of patients with NLR ≥ 2.4 (median OS: 28.5 *vs*. 6.0 mo., $P < 0.001$). Sha et al. conducted a long-term prognostic analysis of 285 patients with gallbladder cancer who underwent cholecystectomy and found that the median OS of patients with NLR < 3.13 was significantly better than that of patients with NLR ≥ 3.13 (median OS: 13.0 *vs*. 8.27 mo., $P < 0.001$); the median OS of patients with PLR < 143.77 was significantly better than that of patients with PLR ≥ 143.77 (median OS: 10.80 *vs*. 10.27 mo., $P > 0.05$). However, the value of NLR and PLR in assessing long-term prognosis after curative resection of pCCA has not been demonstrated. To our knowledge, this is the first multicenter study to evaluate the usefulness of inflammatory markers NLR and PLR as indicators of OS and RFS after curative resection of pCCA.

In this multicenter study, a total of 333 patients underwent curative resection of pCCA. Moreover, the cutoff values obtained by NLR and PLR for predicting 1-year OS were used to group all patients, namely, the NLR cutoff values was 1.68, and the PLR cutoff values was 113.1. There were 178 patients (53.5%) in the high NLR group, 155 patients (46.5%) in the low NLR group, 102

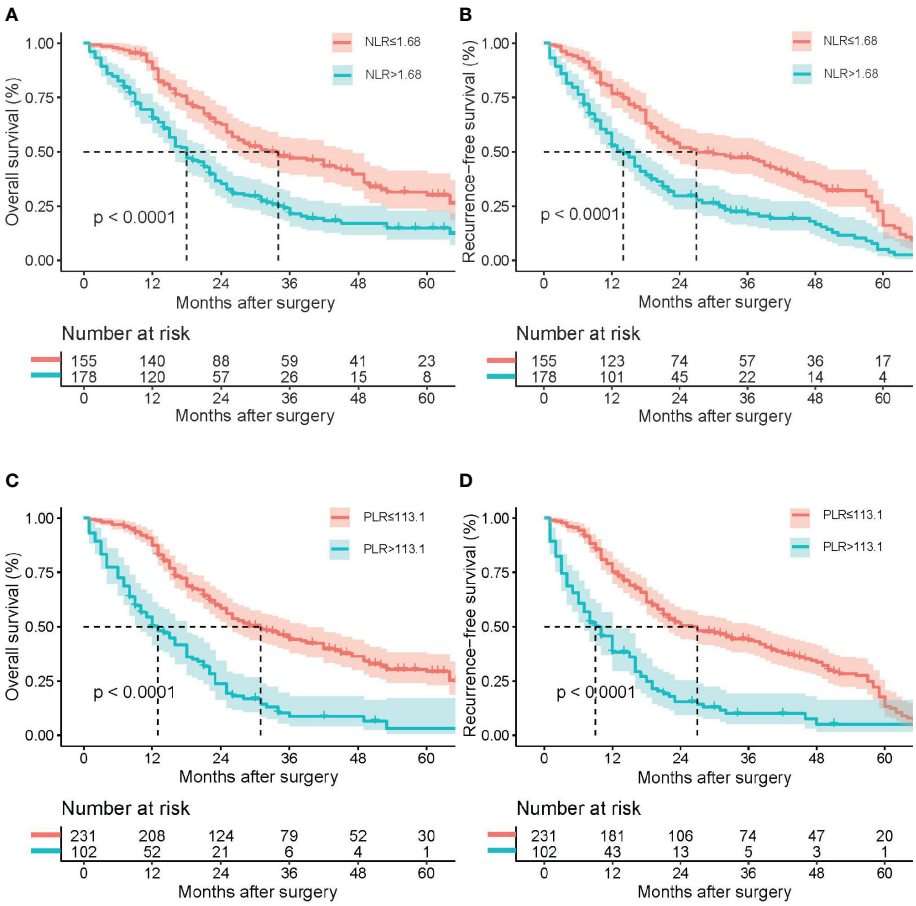

FIGURE 3
Kaplan–Meier survival analysis indicated that patients with NLR ≥ 1.68 had a shorter RFS and OS; patients with PLR ≥ 113.1 had a shorter RFS and OS. Overall survival **(A)** and recurrence-free survival **(B)** curve comparisons between patients with NLR ≥ 1.68 and NLR < 1.68; overall survival **(C)** and recurrence-free survival **(D)** curve comparisons between patients with PLR ≥ 113.1 and PLR < 113.1.

patients (30.6%) in the high PLR group and 231 patients (69.4%) in the low PLR group. In the univariate analysis, the median OS and RFS of patients with a low NLR were significantly better than those with a high NLR (42.2 *vs.* 26.7 mo., $P < 0.001$; 35.5 *vs.* 21.6 mo., $P < 0.001$), and the median OS and RFS of patients with a low PLR were significantly better than those with a high PLR (40.7 *vs.* 17.8 mo., $P < 0.001$; 33.9 *vs.* 15.0 mo., $P < 0.001$). In multivariate Cox regression analysis, NLR and PLR were confirmed as independent risk factors for predicting OS and RFS in patients after curative resection of pCCA.

The mechanism of these phenomena has been confirmed and explained in previous studies (8, 9, 12, 13, 32–34). Neutrophils are the first responders to cell damage, and neutrophil infiltration marks persistent inflammation, which not only causes tissue damage but also, more importantly, promotes tumor progression, metastasis, and angiogenesis. In addition, reactive oxygen species and reactive nitrogen species produced by neutrophils can produce proto-oncogenes, leading to oxidative DNA damage and increasing genetic instability (8). It cannot be ignored that the enzymes produced and released by neutrophils, such as myeloperoxidase, neutrophil elastase, and matrix metalloproteinases, can also promote tumor progression (8). Neutrophils typically produce NETs (neutrophil-extracellular traps) during inflammation. NETs can capture circulating cancer cells (CTCs), and when they are released into the tumor microenvironment, they stimulate tumor cell migration and invasion (8, 9). Platelets also play an important role in promoting tumorigenesis and development. Platelets have been confirmed to promote tumor angiogenesis by releasing p-selectin and vascular endothelial growth factor, and they provide a suitable tumor microenvironment for tumor cell metastasis (12, 13). Platelets can also protect CTCs from being lysed by natural killer cells by encasing tumor cells in thrombi (32). However, as a type of immune cell, lymphocytes can play an important antitumor role. When the number of lymphocytes decreases, the body's resistance to tumor cells decreases

TABLE 3 Univariable and multivariable Cox regression analyses for OS of pCCA patients.

Variables	Comparison	Univariable analyses		Multivariable analyses*	
		P value	HR (95% CI)	*P* value	HR (95% CI)
Age	> 60 *vs.* ≤ 60 years	0.470	1.101 (0.849-1.428)		
Gender	male *vs.* female	0.480	1.101 (0.842-1.440)		
ASA score	> 2 *vs.* ≤ 2	0.617	1.114 (0.729-1.702)		
Comorbidity	yes *vs.* no	0.191	1.217 (0.910-1.632)		
Preoperative jaundice	yes *vs.* no	0.193	1.221 (0.907-1.634)		
ALB	< 35 *vs.* ≥ 35 g/L	0.162	1.212 (0.926-1.586)		
ALT	> 40 *vs.* ≤ 40 U/L	0.263	1.215 (0.864-1.709)		
AST	> 40 *vs.* ≤ 40 U/L	0.505	1.120 (0.802-1.565)		
NLR*	< 1.68 *vs.* ≥ 1.68	< 0.001	1.941 (1.491-2.525)	0.015	1.417 (1.071-1.875)
PLR*	< 113.1 *vs.* ≥ 113.1	< 0.001	2.883 (2.196-3.783)	< 0.001	2.223 (1.671-2.957)
CA 19-9*	> 150 *vs.* ≤ 150 U/L	0.001	1.794 (1.278-2.516)	0.006	1.610 (1.144-2.266)
INR	> 1.15 *vs.* ≤ 1.15	0.211	1.398 (0.827-2.364)		
Cirrhosis	yes *vs.* no	0.612	1.123 (0.717-1.761)		
Chronic hepatitis	yes *vs.* no	0.181	0.720 (0.444-1.165)		
Hepatolithiasis	yes *vs.* no	0.431	1.202 (0.760-1.902)		
Maximum tumor size*	< 3 cm *vs.* ≥ 3 cm	< 0.001	1.735 (1.337-2.252)	0.001	1.576 (1.204-2.062)
Tumor differentiation*	poor *vs.* well/moderate	< 0.001	2.062 (1.491-2.883)	0.218	1.316 (0.851-2.305)
Macrovascular invasion*	yes *vs.* no	0.002	1.568 (1.191-2.065)	0.021	1.416 (1.055-1.902)
Microvascular invasion*	yes *vs.* no	< 0.001	2.201 (1.598-3.293)	0.051	1.620 (0.997-2.632)
Peripheral nerve invasion	yes *vs.* no	0.657	1.074 (0.811-1.413)		
Lymph node metastasis*	yes *vs.* no	< 0.001	2.138 (1.652-2.776)	< 0.001	2.012 (1.531-2.644)
Extent of hepatectomy	major *vs.* minor	0.213	1.207 (0.898-1.621)		

*Those variables found significant at P <.100 in univariable analyses were entered into multivariable Cox regression analyses.
ALB, albumin level; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate transaminase; CA19-9, carbohydrate antigen 19-9; CI, confidence interval; HR, hazard ratio; INR, international normalized ratio; NLR, neutrophil-to-lymphocyte ratio; pCCA, perihilar cholangiocarcinoma; PLT, platelets level; PLR, platelet-to-lymphocyte ratio; RFS, recurrence-free survival; TB, total bilirubin.

accordingly. Previous studies have reported that tumor-infiltrating lymphocytes play a positive role in resisting various advanced malignant tumors (33, 34).

In recent studies, there have been significant differences between the high NLR group and the low NLR group and between the high PLR group and the low PLR group. Before comparative analysis between the two groups, it may not be appropriate to use propensity score matching to examine the relationship between NLR, PLR and long-term oncology results to balance the baseline characteristics because this may lead to an increase in selection biases between the two groups. Therefore, univariate and multivariate Cox regression analyses were used in this study to determine whether high NLR and PLR were independently related to worse OS and RFS after curative resection of pCCA and to adjust for other prognostic risk factors.

With the advent of the era of immunotherapy, immune checkpoint inhibitors have achieved great success in the treatment of almost all solid tumors, bringing hope for tumor patients. Similarly, in related studies on biliary tumors, some clinical drug trials have achieved exciting progress (clinical trial information: NCT03875235 and NCT03875235) (35). In recent years, a PD-L1 receptor inhibitor (EnvafoLimab) has been approved by the FDA for the treatment of biliary tumors. Since both NLR and PLR can reflect immune function, clarifying the relationship between these two markers and prognosis will provide strong support for further exploring the

TABLE 4 Univariable and multivariable Cox regression analyses for RFS of pCCA patients.

Variables	Comparison	Univariable analyses		Multivariable analyses*	
		P value	HR (95% CI)	*P* value	HR (95% CI)
Age	> 60 *vs.* ≤ 60 years	0.115	1.011 (0.997-1.021)		
Gender	Male *vs.* Female	0.353	0.889 (0.692-1.139)		
ASA score	> 2 *vs.* ≤ 2	0.996	1.001 (0.779-1.281)		
Comorbidity	Yes *vs.* No	0.295	1.158 (0.878-1.541)		
Preoperative jaundice	Yes *vs.* No	0.199	1.982 (0.911-1.582)		
ALB	< 35 *vs.* ≥ 35 g/L	0.138	0.823 (0.641-1.072)		
ALT	> 40 *vs.* ≤ 40 U/L	0.077	1.326 (0.971-1.836)		
AST	> 40 *vs.* ≤ 40 U/L	0.350	1.162 (0.851-1.592)		
NLR*	< 1.68 *vs.* ≥ 1.68	<0.001	1.938 (1.511-2.479)	<0.001	1.598 (1.224-2.088)
PLR*	< 113.1 *vs.* ≥ 113.1	<0.001	2.772 (2.121-3.623)	<0.001	2.138 (1.613-2.833)
CA 19-9*	> 150 *vs.* ≤ 150 U/L	0.006	1.516 (1.132-2.047)	0.227	1.210 (0.888-1.649)
INR	> 1.25 *vs.* ≤ 1.25	0.503	1.192 (0.711-1.992)		
Cirrhosis	Yes *vs.* No	0.836	1.050 (0.671-1.639)		
Chronic hepatitis	Yes *vs.* No	0.375	0.822 (0.521-1.280)		
Hepatolithiasis	Yes *vs.* No	0.269	1.286 (0.821-2.005)		
Maximum tumor size*	< 3 cm *vs.* ≥ 3 cm	0.002	1.491 (1.162-1.912)	0.011	1.398 (1.080-1.812)
Tumor differentiation*	poor *vs.* well/moderate	<0.001	1.931 (1.403-2.659)	0.099	1.411 (0.937-2.124)
Macrovascular invasion*	Yes *vs.* No	0.001	1.592 (1.221-2.093)	0.031	1.367 (1.030-1.815)
Microvascular invasion*	Yes *vs.* No	<0.001	2.179 (1.531-3.108)	0.239	1.313 (0.835-2.065)
Peripheral nerve invasion	Yes *vs.* No	0.637	1.071 (0.822-1.389)		
lymph node metastasis*	Yes *vs.* No	<0.001	2.047 (1.593-2.629)	<0.001	1.638 (1.246-2.154)
Extent of hepatectomy	Major *vs.* Minor	0.784	1.039 (0.791-1.364)		

*Those variables found significant at P <.100 in univariable analyses were entered into multivariable Cox regression analyses.
ALB, albumin level; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate transaminase; CA19-9, carbohydrate antigen 19-9; CI, confidence interval; HR, hazard ratio; INR, international normalized ratio; NLR, neutrophil-to-lymphocyte ratio; pCCA, perihilar cholangiocarcinoma; PLR, platelet-to-lymphocyte ratio; PLT, platelet level; RFS, recurrence-free survival; TB, total bilirubin.

formulation of personalized immunotherapy programs in patients with hilar cholangiocarcinoma.

This study has several limitations. First, it is a retrospective study, which will inevitably lead to bias in data collection. Second, the patients' NLR and PLR values were calculated by a single measurement at admission, imposing some uncertainty. Third, the patients in this study were all from China, so data from Western patients was lacking. Therefore, the applicability of this conclusion to Western patients needs to be verified. Fourth, the number of patients included in this study was small; although it was a multicenter study, there were only 333 patients, possibly related to the relatively low incidence of pCCA. In the future, we will work with individual centers to provide a higher level of evidence.

In conclusion, our study suggests that NLR and PLR are potential prognostic factors for long-term prognosis in pCCA patients undergoing curative resection. After curative resection, these ratios are strongly correlated with survival, readily available, and economically determined. This study has strong clinical implications: higher NLR and PLR indicate a poor prognosis, so more attention should be given to patients with such values of NLR and PLR. It may be possible to minimize the levels of these two markers to improve the prognosis of patients,

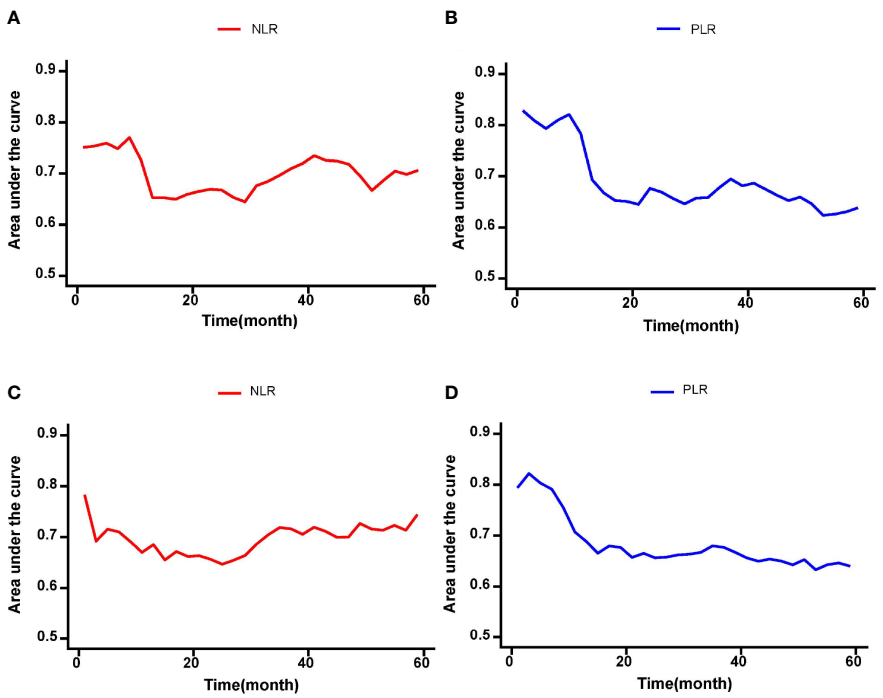

FIGURE 4
The time-dependent ROC curves of the NLR and PLR for OS and RFS in pCCA patients. **(A-D)** NLR and PLR were useful in effectively predicting long-term outcomes such as OS and RFS according to the results of time-dependent ROC analysis.

but further confirmation is needed. Once these findings have been validated in a larger prospective cohort, NLR and PLR markers could be used to help guide the clinical management of patients with pCCA.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Southwest Hospital of Chongqing, China (No. KY2021129). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conception—Z-YC, YJ, YG. **Study design**—M-YG, Z-PL, H-SD. **Administrative support**—Z-YC, YG. **Data collection and acquisition**—S-YG, S-YZ, X-YC, J-HZ, Y-HL, X-CL, H-NF, W-YC, Z-RW, X-YY, JB. **Data analysis**—M-YG, Z-PL, Y-QZ. **Manuscript preparation**—M-YG, Z-PL, YP, J-YW, XW. **Critical revision**—Z-YC, YJ, YG. **Final approval of manuscript**—All authors. M-YG, Z-PL, YP, J-YW, and XW contributed equally to this work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Treatment of hepatic venous system hemorrhage and carbon dioxide gas embolization during laparoscopic hepatectomy *via* hepatic vein approach

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With the improvement of laparoscopic surgery, the feasibility and safety of laparoscopic hepatectomy have been affirmed, but intraoperative hepatic venous system hemorrhage and carbon dioxide gas embolism are the difficulties in laparoscopic hepatectomy. The incidence of preoperative hemorrhage and carbon dioxide gas embolism could be reduced through preoperative imaging evaluation, reasonable liver blood flow blocking method, appropriate liver-breaking device, controlled low-center venous pressure technology, and fine-precision precision operation. In the case of blood vessel rupture bleeding in the liver vein system, after controlling and reducing bleeding, confirm the type and severity of vascular damage in the liver and venous system, take appropriate measures to stop the bleeding quickly and effectively, and, if necessary, transfer the abdominal treatment in time. In addition, to strengthen the understanding, prevention and emergency treatment of severe CO2 gas embolism in laparoscopic hepatectomy is also the key to the success of surgery. This study aims to investigate the methods to deal with hepatic venous system hemorrhage and carbon dioxide gas embolization based on author's institutional experience and relevant literature. We retrospectively analyzed the data of 60 patients who received laparoscopic anatomical hepatectomy of hepatic vein approach for HCC. For patients with intraoperative complications, corresponding treatments were given to cope with different complications. After the operation, combined with clinical experience and literature, we summarized and discussed the good treatment methods in the face of such situations so that minimize the harm to patients as much as possible.

KEYWORDS

laparoscopy, hepatectomy, hepatic vein, hemorrhage, gas embolism

Introduction

Liver cancer ranks fifth in cancer incidence and fourth in cancer-related mortality worldwide. And the liver is the sixth primary cancer site (1). Among the many types of liver cancer, HCC occupies the absolute leading number, accounting for 80-90% of primary liver cancer (2).With the development of minimally invasive surgery, laparoscopic hepatectomy (LH) indications expand. The hepatic vein is widely used to guide the approach because of its prominent dissection position (3).Laparoscopic hepatectomy may improve the short - and long-term prognosis after hepatectomy (4). Although there were no significant differences in complication rates or tumor outcomes compared with open hepatectomy, Laparoscopic hepatectomy has the advantages of less blood loss, lower anesthesia dose and shorter hospital stay. Accurate laparoscopic segmentectomy can reduce the abdominal incision and damage to the patient's body, and it can increase patients' chances of potential surgery to deal with the recurrence of the disease. Laparoscopic hepatectomy is the best choice under the premise of ensuring the function of the liver and not reducing the curative effect of the operation (5, 6). Therefore, Laparoscopic hepatectomy has been considered the great option for HCC resection in recent EASL guidelines (7).At present, LH has been widely used in the surgical treatment of a variety of benign and malignant liver diseases, and is expected to replace traditional open surgery, becoming the "gold standard" for surgical treatment of certain liver diseases (8). However, intraoperative hemorrhage and carbon dioxide gas embolization are still the biggest difficulties in LH (9, 10). Intraoperative hemorrhage not only increases the risk of complications caused by blood transfusion, but also relates to the high recurrence rate and low survival rate in patients with malignant tumors (11). Hemorrhage during LH includes hemorrhage from the Glisson system and hemorrhage from the hepatic venous system. Considering that the portal vein and hepatic artery branches of the Glisson system are thick, surrounded by Glisson sheaths, the wall is easily contracted and not easily torn after injury, and it is easier to clip and suture blood vessels by Pringle Maneuver to block the first hepatic portal blood flow, therefore, it is relatively simple to treat bleeding. It is well known that the hepatic venous system includes the left liver, the liver, the right hepatic vein and its branches, the short hepatic vein and the inferior vena cava. The difficulty in controlling hepatic venous hemorrhage is related to several reasons. First of all, the hepatic venous system has a large lumen, a thin wall, a large number of branching holes, and is easily damaged and torn. Second, the hepatic vein lacks a valve device that prevents blood reflux. Finally, the hepatic vein wall is not easily contracted in the liver parenchyma. In addition to the risk of major bleeding after injury, there is still a risk of CO2 gas embolism (12). Moreover,treating intraoperative bleeding in patients with tumors is even more difficult, since the vasculature at the tumor site is more permeable due to invasion of tumor cells (13). In the case of unintentional injury, tributaries of the hepatic veins may be the main source of bleeding. Prevention of venous injury remains a challenge, as the most suitable technique has not been established, but the risk of venous injury can be effectively reduced by accessing or exposing the anterior or posterior side of the hepatic vein prior to dissection of the lateral side (14). GE frequently occurs during laparoscopic hepatectomy, although most episodes of grade 1 embolism seem to be harmless (15). Severe CO2 embolization can quickly cause respiratory and circulatory dysfunction in patients, and if the treatment experience is not appropriate, it can cause serious consequences such as hypoxemia, heart failure, arrhythmia and even death. Laparoscopic surgery can be complicated by gas embolism, and although the incidence of this disease is estimated to be as low as 0.002% to 0.02%, the mortality rate is as high as 50%.The characteristic manifestation of gas embolism is cyanosis of the head and neck with a millwheel cardiac murmur due to obstruction of inflow to the right side of the heart. Signs of diagnosis include arrhythmia, hypoxia, and a sudden decrease in end-tidal carbon dioxide. However, the clinical manifestations of embolism in the subjects were not obvious. This also indicates the high risk of carbon dioxide embolism during laparoscopic surgery (16).

Therefore, prevention and control of hepatic venous system hemorrhage during LH and timely treatment of severe CO2 gas embolism caused by venous hemorrhage are the key to reducing perioperative complications of LH and promoting postoperative recovery. In the last two years, our center completed 60 cases of laparoscopic anatomical hepatectomy (type of hepatic segment resection as seen in Table 1, and clinical and surgical data in Table 2). This article will be based on the author's institutional experience, combined with relevant literature to explore the hepatic venous system hemorrhage and CO2 gas embolization during the LH.

Materials and methods

Patients and methods

This retrospective study was approved by the Institutional Review Board of Changzhou First People's Hospital. All study participants gave written informed consent for the use of their clinical records. A total of 60 patients who received laparoscopic anatomical hepatectomy of hepatic vein approach for HCC from January 2019 to December 2020 at the Changzhou First People's Hospital were retrospectively reviewed from our department's prospective surgical database. A total of 60 patients underwent laparoscopic hepatectomy through the hepatic vein approach, according to the location of liver segment resection, there are 13 cases of II and III segments, 23 cases of II, III and IV, 7 cases of

TABLE 1 Laparoscopic hepatectomy *via* hepatic vein approach(60 cases).

Resection of hepatic segment	Cases
II, III	13
II, III, IV	23
V, VI, VII, VIII	7
V, VIII	2
VI, VII	4
IV	2
VII	3
VIII	3
I	3
Total	60

V, VI, VII and VIII, 2 cases of V and VIII, 4 cases of VI and VII, 2 cases of IV, 3 cases of VII, 3 cases of VIII and 3 cases of I. According to the disease type, there are 31 cases of hepatocellular carcinoma, 21 cases of intrahepatic bile duct stones, 3 cases of focal nodular hyperplasia, 3 cases of liver metastatic carcinoma, 1 case of hepatoblastoma, and 1 case of Inflammatory pseudotumor of the liver.

Surgical methods: After general anesthesia, the patient was placed in horizontal position, in which the right posterior lobe of the liver was excised with the right side raised and the right forearm fixed in the anesthesia frame.The Trocar has 4-6 Wells in total, and the location is fanned out according to the target liver segment. The observation and Pringle blocking holes are located around the umbilicus, and the main operating hole is placed on the extension line of the liver section (Figure 1). the intra-abdominal pressure was set to 12mmHg (1mmHg =0.133kPa), and the extrahepatic preset blocking band: the nylon band was pulled out of the blocking hole around the posterior two ends of the first hepatic hilum, and the plastic blocking tube was used to achieve repeated blocking and loosening *in vitro* in combination with the vascular clamp. The plane of the severed liver was obtained by intraoperative ultrasound localization of the main hepatic vein (Figure 2A), and the perihepatic bands were fully dissociated during right hemihepatectomy or right posterior lobe hepatectomy.During the operation, Pringle "15+5" mode (blocking the blood flow into the liver for 15min, releasing the blood flow for 5min, and repeating the circulation) was used to block the blood flow into the liver, and then the liver was broken.

The surgeon stood on the right side of the patient, held the ultrasonic knife in the right hand to cut the liver, and advanced from the tail side to the head side (Figure 2B). Among them, the ultrasonic knife was directly cut off the pipeline with diameter less than 1mm, the titanium clip was used to clamp the 1-2mm pipeline, and the Hem-O-LOCK was used to clamp the >2mm pipeline. The liver pedicle or hepatic vein root could also be cut off with a cutting closure device (Figure 2D).When the bile duct needed to be removed, the bile duct was dissected and closed. In the process of liver amputation, hemostasis was stopped by using an aspirator and a bipolar electrocoagulation section Surgicel compression hemostasis is used for the rupture of hepatic vein less than 3mm, a 4-0 prolene suture was used for hemostasis with the rupture>3mm (Figure 2C). The direction of intraoperative liver resection was from the foot to the head, from shallow to deep, and with the help of intraoperative ultrasound guidance, the main hepatic vein was gradually exposed. At the same time, intraoperative anesthesia should be combined with control of central venous pressure (CVP), and CVP <5cm H2O is safe for LH.

Results

1. A total of 60 patients underwent laparoscopic hepatectomy *via* hepatic vein approach, and the specific surgical methods are shown in Table 1. The images of different segmentectomy are shown in Figures 2, 3. During the operation, the left, middle or right hepatic veins were clearly exposed according to the needs of the target hepatic segment resection.

2. In this group, 36 cases were intrathecal occlusion and 24 cases were extrathecal occlusion, among which 51 cases were combined with Pringle (15 + 5min) to block the first hilar for a maximum of 5 times, and 22 cases were dissected with the second hilar combined with hepatic vein pre-occlusion during operation. The operation time was 150.17 ± 68.30 min, the intraoperative blood loss was 230.59 ± 290.34 mL, and there was no conversion to open surgery (Table 2).

3.Serious complications occurred in 13 cases.There were 5 cases of hepatic vein hemorrhage, and one of them was the rupture of cutting stapling device in the right hepatic vein root, and the nail used for fixing is loosened.The bleeding stopped after the vessel was sutured. 4 cases of carbon dioxide gas embolism were ameliorated by suspension of pneumoperitoneum, head high and foot low right elevation, positive end-expiratory pressure ventilation, and proper hemostasis of hepatic vein (Table 2). ALT and AST were (205.67 ± 223.04) U/L and (189.91 ± 194.04) U/L on the first day after operation, and (158.63 ± 153.90) U/L and (63.28 ± 64.63) U/L and (63.28 ± 64.63) U/L on the third day after operation.There were no cases of abdominal bleeding and 4 cases of bile leakage, which were cured by conservative treatment. No reoperation or operative death occurred.The postoperative hospital stay was 7.49 ± 5.30 days.

Discussion

LH started relatively late, and it could only be performed in a few centers in the 1990s. However, with the technological innovation, the improvement of surgical techniques and the

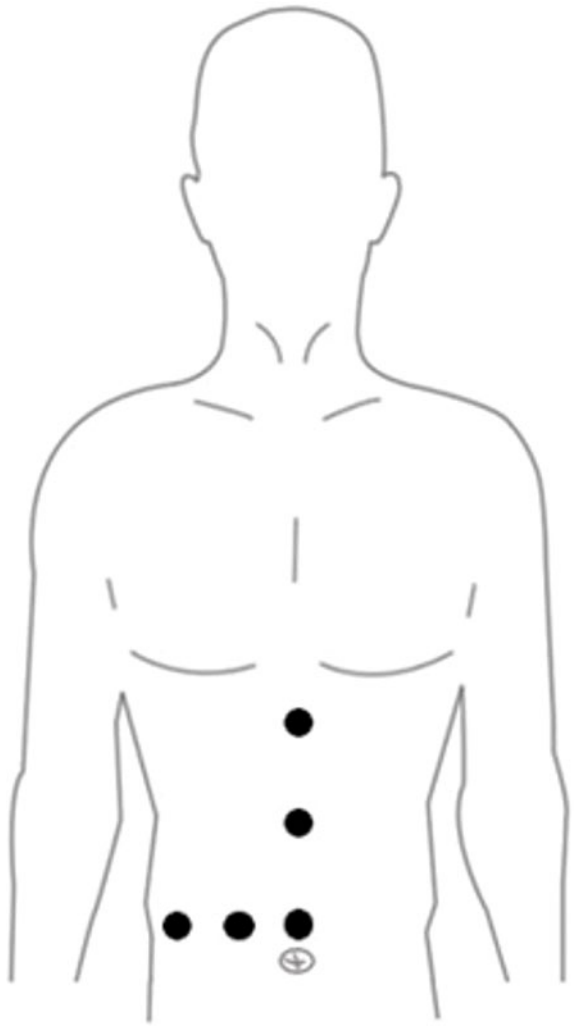

FIGURE 1
Port sites.

accumulation of surgeons' experience, laparoscopic hepatectomy has made great progress in minimally invasive liver surgery in the late 21st century (17). Liver resection *via* hepatic vein approach was first advocated by Makuuchi in Japan, and has become one of the standards of anatomical liver resection. He proposed that the intrahepatic marker for anatomical hepatectomy is the hepatic vein,accurate anatomy and exposure of intraoperative hepatic vein is the key to laparoscopic anatomic hepatectomy through hepatic vein (18). According to a recent international literature review, LH is associated with less blood loss and lower postoperative morbidity compared with open hepatectomy, but does not differ significantly in terms of tumor outcome (19). The difficulty lies in the prevention and treatment of intraoperative hepatic vein bleeding, gas embolism and other complications. "Tenting sign of hepatic veins" is an important anatomical knowledge that can help us reduce bleeding during surgery (20). Previous studies have shown that keeping PP below 12mmhg may reduce the occurrence of carbon dioxide embolism (21).In this study, when intraoperative CO2 embolism occurred, pneumoperitoneum suspension, head high foot low right elevation, and positive end-expiratory pressure ventilation were used to rapidly improve the situation. After reading a large number of literatures, I conclude that the most important treatment for intraoperative CO2 embolization is to reduce pneumoperitoneum pressure, control CVP, and increase ventilation. Takechi K's paper addressed CO2 embolism as follows: 1. Lower pneumoperitoneum pressure, but proceed with laparoscopic surgery. 2. Abandon the Pringle technique. 3. The fraction of inhaled oxygen was increased to 1.0, and intravenous phenylephrine (0.1 mg) was administered (22). But interestingly, intraoperative bleeding and carbon dioxide

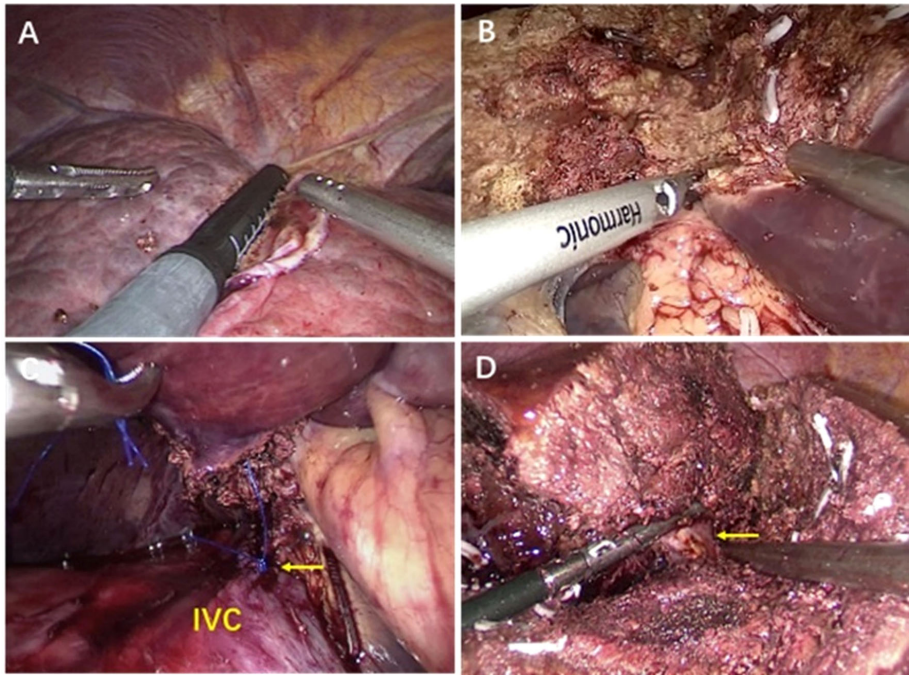

FIGURE 2
(A) By intraoperative ultrasound to localize liver tumors. **(B)** Transection of liver tissue with ultrasonic scalpel. **(C)** Used 5-0 prolene to suture laceration of retrohepatic inferior vena cava(RIVC) under laparoscope. **(D)** Laparoscopic separation of the VIII.

embolism seem to be the opposite of the coin. The Second International Consensus Conference on Laparoscopic Hepatectomy, based on 54 publications, made the following recommendations for intraoperative bleeding control: 1. Use a high pressure pneumoperitoneum of 10-14 MMHG. 2. Use a CVP of less than 5mmHg (23).Moreover,in order to improve the postoperative prognosis of patients and reduce the intraoperative risk, I think the following steps are essential.

Preoperative accurate assessment

Most patients with laparoscopic hepatectomy in China have a background of hepatitis and cirrhosis, and have poor liver reserve and tolerance to ischemia-reperfusion injury, so they are more likely to bleed during liver resection. Accurate assessment of the patient's liver function, the relationship between the lesion and important blood vessels before surgery is essential to prevent

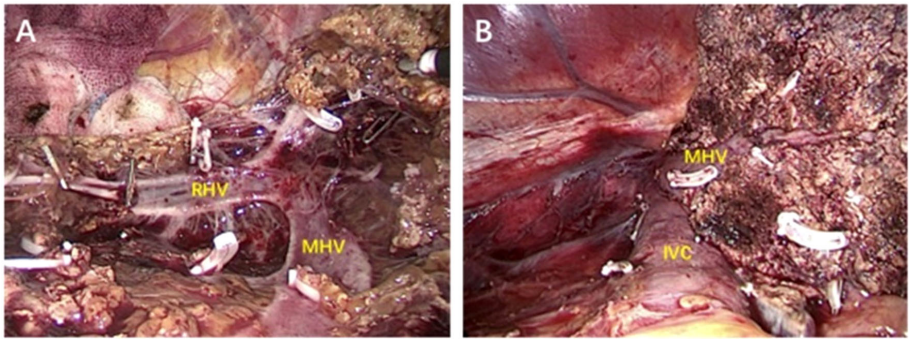

FIGURE 3
(A) Resection of the segment VIII, the right hepatic vein (RHV) and middle hepatic vein (MHV) were exposed during the operation. **(B)** After right lobe hepatectomy, the inferior vena cava (IVC) and middle hepatic vein (MHV) were exposed.

TABLE 2 Clinical characteristics of 60 patients with laparoscopic hepatectomy.

Clinical characteristics	Value
Age	55.60 ± 14.35
Sex	
Male	22 (36.67%)
Female	38 (63.33%)
Operation time	150.17 ± 68.30
Intraoperative blood loss	230.59 ± 290.34
Postoperative hospital stay	7.49 ± 5.30
Major intraoperative events	
Suture of hepatic vein	5 (8.33%)
Carbon dioxide embolism	4 (6.67%)
Postoperative complications	
Bleeding	0 (0%)
Bile leakage	4 (6.67%)

intraoperative hepatic venous bleeding. At present, it is mainly evaluated by ultrasound (Figure 2A), CT, MRI and other instruments to determine the extent of liver resection and the anatomical relationship of the main liver pipeline, especially the hepatic vein system, and then select the best surgical plan.

Three-dimensional virtual liver technology has been able to display intrahepatic vessels with a diameter of more than 1 mm, especially for the details of the intrahepatic vasculature (24). For large-scale liver resection, special site hepatectomy and other complex LH involving deep hepatic parenchyma, I recommend three-dimensional visual assessment, and carry out three-dimensional reconstruction based on two-dimensional imaging data to comprehensively evaluate the spatial stereo relationship between the lesion and the hepatic artery, portal vein, bile duct, hepatic vein or inferior vena cava (11). In addition, preoperative simulated segmental hepatectomy can be performed by using virtual surgical software to predict the major pipeline structures and complex important dangers that may be encountered during the actual operation of laparoscopic liver resection. It is necessary to cope with the dangerous parts that are prone to bleeding and the trunk and important branches of the hepatic vein that may be involved in order to effectively prevent the risk of hemorrhage of the hepatic venous system during operation.

Methods to block blood flow in the hepatic vein system

Compared with traditional open liver resection, once hepatic venous system hemorrhage occurs during LH, the treatment is relatively more difficult (25). During the laparoscopic surgery, surgeons can not use the conventional methods such as top, pressure, pinch and other conditions under laparotomy to control bleeding, and it is difficult to complete the precise suture to stop bleeding in time, moreover, the bleeding will also contaminate the lens, affect the visual field, which further increase the difficulty of hemostasis. In order to reduce the risk of surgery and prevent hepatic venous system hemorrhage, appropriate hepatic blood flow blockage should be selected during surgery to avoid passive treatment after hemorrhage.

The first hepatic portal blood flow blockage can directly reduce the hepatic venous return blood volume, rapidly reduce the hepatic sinus, hepatic venous pressure and central venous pressure. In addition to effectively controlling the Glisson system bleeding, it is also effective in reducing hepatic venous system hemorrhage. Some scholars have pointed out that the anatomical separation of the second hepatic hilum may damage the hepatic vein, which may not only cause major bleeding, but also increase the incidence of CO2 gas embolism. Therefore, the suture of the liver parenchyma is more reliable than the separation of the second hepatic hilum outside the liver parenchyma (26). Blocking the third hepatic hilum should first fully dissipate the entire liver. The short hepatic vein and the right posterior inferior vein were separated from the bottom to the top and from the right to the left. The proximal end was clamped with an absorbable clip, and the distal end was ligated and disconnecte (27). Chen's simple total hepatic blood flow blocking technique (Pringle method + lower hepatic inferior vena cava blockage) can significantly reduce the blood flow of the hepatic vein and the superior and inferior vena cava, rapidly reduce the pressure, and obtain a similar whole hepatic blood flow blockage. The clinical effect can safely and effectively control the hepatic section hemorrhage during operation, and the operation is simple and easy, which is conducive to clear and accurate liver resection (28).

Application of various laparoscopic liver resection instruments

The removal of liver parenchyma in LH is inseparable from various instruments. The effective disconnection of hepatic veins and branches in liver parenchyma is one of the keys to prevent and control hepatic venous system hemorrhage. The author's institution mainly uses the ultrasonic scalpel (Figure 2B), Cavitron Ultrasonic Surgical Aspirator (CUSA) and endoscopic GIA (Endo-GIA) for liver parenchyma resection.

Ultrasonic scalpel is mainly used to cut thin layer of liver tissue, can close the blood vessel with diameter <3mm without damage, while the blood vessel with diameter >3mm needs to be clamped with titanium clip (29). By oscillating to rupture of the liver cells, thereby retaining the intact structure of the blood vessels and bile ducts, the ultrasonic scalpel has the advantages of

shortening the time of the liver parenchyma, low thermal damage, and less bleeding (30). The method of using the ultrasonic knife to cut off the liver is "small-mouth engulfment, layer-by-layer advancement". When the liver tissue is condensed and cut, the cutter head is used for clamping, crushing, pushing and separating. The metal working surface of the cutter head should always be in the visible state, try to stay away from blood vessels, and do not blindly penetrate the liver parenchyma to cause blood vessels to burn.

CUSA is a versatile device that destroys and absorbs tissue cells with high water content, while highly elastic tissue with high collagen content (such as blood vessels and biliary system) is not destroyed, thus reducing the damage to normal tissues to the lowest (31). CUSA is especially suitable for deep liver parenchyma, which is conducive to fine dissection of the pipe structure and disconnection. The use of CUSA should select the appropriate power based on the pathology of the liver parenchyma. For the important pipeline structure on the section, especially the hepatic vein branch, it should be fully dissected and dissected to achieve full-dimensional nakedness. After confirming the diameter of the tube and walking, then the vessel clamp is properly clamped and then disconnected. It is forbidden to cut the blood vessel with an ultrasonic scalpel without fully exposing the blood vessel, or cut it with the blood vessel clamp clamping half of the blood vessel.

Endo-GIA staple cartridges can be divided into white nails, blue nails and golden nails according to the different nail heights. In the operation, different nail cartridges can be used to disconnect the traffic branches in the liver parenchyma according to the thickness of the liver tissue. Endo-GIA can disconnect liver tissue, blood vessels and biliary branches at one time, speeding up the operation and increasing the safety of surgery (32). (Figure 2D). For patients with partial vascular variability, in order to avoid accidental injury, laparoscopic ultrasound-assisted positioning can be used to determine the location of the vessel before the Endo-GIA is used to disconnect the vessel.

Intraoperative fine operation to prevent hepatic venous system hemorrhage and CO2 gas embolism

Hepatic veins vary greatly in walking in the liver, making it difficult to find a fixed treatment pattern. The important pipeline structure that is difficult to confirm during operation should be carefully identified with the anatomical landmark of the liver surface and the ischemic boundary line after regional hepatic blood flow blockade. If necessary, combined with laparoscopic intraoperative ultrasound (Figure 2A), etc. to prevent accidental injury.

When dissecting the liver and treating the hepatic vein root and the short hepatic vein, the interstitial space should be identified, and the correct direction, angle and strength should be grasped. The operation should be gentle, avoid forced separation, and puncture the blood vessels. It has been reported that the second hepatic hilum is dissected and the corresponding hepatic vein is sutured through the liver before the liver is cut. We have also tried a few cases, and the effect of stopping bleeding during the operation is obvious. During LH, attention should be paid to maintaining a moderate tension in the section and cleaning the field. If the tension is too small, the section cannot be unfolded, affecting the visual field, exposure and operation; if the tension is too large, the hepatic vein branch of the section may be torn to cause bleeding or CO2 gas embolism.

Good vision is the premise of laparoscopic operation. During the operation, the surgical field should be kept clean and dry, avoiding smoke and blood. The lens holder should adjust the lens angle at any time to avoid collision between the lens and the operating instrument and the lens. The suction device adopts a point suction or flushing method to ensure sufficient pneumoperitoneal pressure and operation space while sucking up blood and smoke. Blind operation in the "blood pool" should be avoided in case of hepatic venous system hemorrhage, otherwise the hepatic vein trunk may be damaged, resulting in fatal bleeding and severe CO2 gas embolism.

Controlled low central venous pressure technology

Low central venous pressure (LCVP) technology refers to reducing the pressure of hepatic sinuses and intravenous, reducing the pressure gradient inside and outside the blood vessel wall, thereby reducing the amount of bleeding in the process of liver substantive separation, and reducing postoperative blood transfusion, shortening hospital time, reducing postoperative complications, etc (33). However, in LH, the safety and feasibility of LCVP application is still controversial due to pneumoperitoneal pressure and the risk of potential CO2 gas embolism. Animal experiments by Jayaraman et al (12). showed that the incidence of air embolism was positively correlated with the ratio of pneumoperitoneum pressure and central venous pressure. When the ratio increased, the incidence of air embolism increased significantly. Therefore, the balance of pneumoperitoneum pressure and hepatic venous pressure is one of the key factors determining hepatic venous system hemorrhage during LH. When the pneumoperitoneum pressure is lower than the hepatic venous pressure, hepatic venous hemorrhage occurs. Otherwise, CO2 gas embolism occurs. Kobayashi S et al. 's experiment showed that the probability of pulmonary gas

embolism increased when the central venous pressure was lower than the intra-abdominal pressure (34).

Reducing central venous pressure is mainly achieved by limiting the amount of infusion, diuresis, and expansion of peripheral blood vessels. In the liver resection, the use of head high and low feet supine position can reduce the blood flow of the lower extremity vein and peripheral vein, which is helpful for reducing central venous pressure and reducing bleeding. There is no uniform standard for reducing central venous pressure. Liu Zhe et al. (35)believe that during the process of hepatic parenchymal resection, as long as there is no large vein and its branch damage, it is relatively safe to control the central venous pressure at 0-5 cmH2O, which can reduce the bleeding during LH. It should be noted that due to the influence of pneumoperitoneal pressure and body position during LH, the value of central venous pressure monitored during surgery is generally inaccurate and can only be used as a reference. Comprehensive judgment should be made based on clinical features such as oozing blood in the operation section, degree of filling of the hepatic vein and inferior vena cava, and the opinions of the anesthesiologist.

Treatment of hepatic venous system hemorrhage

If bleeding occurs accidentally during LH, the surgeons should keep calm, accurately and timely determine the source of the bleeding, and take appropriate measures to quickly and effectively stop bleeding. Hepatic venous system hemorrhage is characterized by a darker color and a “pulsed” gush. Hepatic vein accidental injury should immediately block the first hepatic portal blood flow into the liver. The left hand uses the device to temporarily compress the bleeding site to reduce bleeding. The assistant uses the aspirator to quickly and accurately remove the blood, clearly revealing the blood site and the degree of blood vessel damage. If it is a small vein branch bleeding in the liver section, bipolar electrocoagulation can be used to stop bleeding. For hepatic vein trunk or larger branch avulsion, rupture and hemorrhage, if the rupture is small, hemostatic can be stopped by partial compression such as gauze or hemostatic cotton. For hepatic vein trunk or larger branch avulsion, rupture and hemorrhage, if the rupture is small, hemostatic can be stopped by partial compression such as gauze or hemostatic cotton. If the rupture is slightly larger, after separating the liver tissue surrounding the damaged blood vessel and fully exposing the vein trunk and branches, clip the vessel at both ends of the rupture, or repair the ruptured vein with a 4-0 or 5-0 Prolene suture (Figure 2C).

It should be noted that after determining the bleeding site do not blindly clamp or largely stitch to stop the bleeding, should try to dissect the exposed blood vessel trend, accurately determine the source of bleeding, and its pipe diameter, walking, crack position, size, etc., and then choose the appropriate method to deal with. In general, most bleeding can be controlled and treated under laparoscopy. For the hepatic vein root and inferior vena cava laceration, it is recommended to quickly fill with gauze, and promptly turn to open the laparotomy.

Treatment of severe CO2 gas embolism during operation

LH often involves important branches of the liver vein, and surgeons are mostly accustomed to using higher abdominal pressure and lower CVP to help reduce intraoperative bleeding, which makes CO2 easier to enter the cavity vein system, thereby increasing the incidence of CO2 embolism. Especially for laparoscopic hepatectomy, the cross-section is difficult to expose, the liver parenchyma is deep in the liver or the right hepatic vein branch, and the operation time is longer, which leads to a significant increase in the probability of severe CO2 gas embolism during surgery.

In our institution, there were 4 patients with typical CO2 gas embolism due to hepatic vein trunk or branch injury during laparoscopic liver resection (Table 2), which showed that arterial blood pressure dropped rapidly to 80/50 mmHg without bleeding or only a small amount of bleeding, the blood oxygen saturation dropped below 80%, and the end-expiratory C02 partial pressure (EtCO2) rapidly dropped below 25 mmHg. By suspending the operation, using gauze or hemostatic material to urgently compress and fill the venous breach, reducing the pneumoperitoneum pressure or changing to no pneumoperitoneum state, using the head low foot high position, changing the ventilation mode to end-expiratory positive pressure ventilation (PEEP), increasing the amount of fluid, increasing the central venous pressure, the abnormal indicators began to return to normal after about 3-10min. The treatment in the paper of Hou W et al. is as follows: pneumoperitoneus is stopped, Trendelenburg position that facilitates the flow of gas into the apex of the right ventricle and prevents it from entering the pulmonary artery (36) is adjusted, and air bubbles are released from the central line (37).In view of the serious consequences that CO2 gas embolism can cause, we believe that the possibility of CO2 gas embolism should be considered in patients with no significant hemorrhage during surgery but accompanied by sudden hemodynamic changes, or a decrease in EtCO2, or spO2. Among above, the early warning consciousness of the surgeon, the roving nurse and the anesthesiologist is the key to early detection of severe CO2 gas embolism. Second, TEE can quickly help diagnose embolism and determine the extent and location of embolism (37).

In short, with the deep understanding of liver imaging and anatomy, the improvement of laparoscopic technique, the accumulation of surgical experience and the continuous updating of surgical instruments, the treatment of hepatic

venous system hemorrhage and severe CO2 gas embolism during LH operation will be further improved. However, in view of the tearing of the main trunk or important branches of the hepatic vein, it not only causes dangerous bleeding, but also may cause CO2 gas embolism to affect the body's circulation which may lead to fatal complications. It is recommended that LH should be performed in larger medical centers by surgeons with experience of laparoscopic surgery.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Third Affiliated Hospital of Soochow University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conception and design: ZQ, Y-FD, and X-ZH. Data collection: K-JW, J-WF, D-SS and JC. Writing the article: ZQ, K-JW, J-WF, D-SS, JC, Y-FD, Y-XC, and D-LS. Critical revision of the article: Y-FD, and X-ZH. Final approval of the article: ZQ, K-JW, D-SS, JC, Y-XC, D-LS, Y-FD, and X-ZH. Statistical analysis: ZQ, K-JW, D-SS and JC. Obtained funding: ZQ and Y-FD. Overall responsibility: Y-FD. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Characteristics of multicystic biliary hamartoma: A case report

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Introduction: Multicystic biliary hamartoma (MCBH) is a very rare hepatic benign neoplasm that manifests as a localized cystic-solid mass. Only 17 cases have been described in the literature to date. MCBH diagnosis is currently dependent on imaging and pathology following surgical resection and no precise standards are in place.

Case Presentation: This case study involves a middle-aged male patient with a history of drinking but no other liver diseases. A routine ultrasound examination showed a 6.0 × 5.5 cm inhomogeneous echo mass in the right lobe of the liver. The patient experienced no discomfort or other symptoms, and blood tests were normal. Imaging revealed a localized cystic-solid neoplasm in segment 6 of the liver that did not have the features of a malignant tumor. Surgical resection was performed. Based on imaging, macroscopic examination, and histological results, a final diagnosis of MCBH was made.

Conclusion: The imaging and pathological features of MCBH were summarized based on the published case reports to date. As a non-invasive examination, the imaging features will aid in the diagnosis of MCBH. Furthermore, these features, along with tumor size and patient symptoms, will facilitate clinicians in selecting surgical resection or follow-up for individual patients.

KEYWORDS

liver, cystic lesion, hamartoma, multicystic biliary hamartoma, operation

Introduction

Patients with hepatic neoplasm are frequently encountered in our clinic. Common causes include hepatocellular carcinoma, cholangiocarcinoma, secondary malignant liver tumors, hemangioma, and abscesses. Diagnosis is dependent on whether there is chronic liver disease, a history of malignant tumors, positive tumor markers, particular imaging features, and pathological manifestations. Some rare hepatic cystic lesions, including mesenchymal hamartoma (HMH), Von Meyenburg's complex (VMC), Caroli's disease, Biliary cystadenoma, ciliated hepatic foregut cyst (CHFC), intraductal papillary neoplasm of the bile duct (IPNB), are also encountered.

Multicystic biliary hamartoma (MCBH) is a very rare hepatic localized cystic–solid neoplasm. MCBH diagnosis is still based on the imaging and pathological characteristics of surgically resected specimens due to a lack of characteristic diagnostic criteria in imaging, effective serological markers, or genetic detection. This case study in a 44-year-old male patient describes the eighteenth reported case of MCBH. Since this was considered a focal benign neoplasm, surgical resection was performed. A diagnosis of MCBH was made using a combination of imaging, macroscopic examination, and histological results.

In 2010, Ryu Y et al. (1) first described the imaging features of MCBH. In the present report, all published cases of MCBH to date were reviewed, and the imaging and histological features of MCBH were summarized. Importantly, this case report focused on imaging characteristics that would aid the diagnosis of MCBH by non-invasive examination.

Case report

This case was a 44-year-old male patient. During his routine physical examination, an approximately 6.0 × 5.5 cm inhomogeneous echo mass was found incidentally in the right lobe of the liver by abdominal ultrasound. The patient denied any accompanying symptoms such as anorexia, abdominal distension or pain, fever, or weight loss. He had a 5-year history of hypertension and took felodipine tablets to control blood pressure. The patient had a 20-year drinking history, equivalent to about 40 g ethanol/day. He had no history of intravenous drug use, exposure to herbal medicines or health care products, or surgical and familial genetic disease. Routine blood analysis was conducted and the values for various tests —liver and kidney function, coagulation function, and tumor markers (alpha-fetoprotein, carcinoembryonic antigen, and carbohydrate antigen 19-9)—were within the normal range. Serological tests for hepatitis B and hepatitis C were negative. Autoantibodies related to autoimmune liver disease, thyroid function, and ceruloplasmin were within the normal range. Physical examination showed no positive disease indicators.

The patient then underwent an imaging examination. A second ultrasound revealed multiple small irregularly shaped hypoechoic masses with slightly hyperechoic septae in segment 6 of the liver (S6), and a total size of approximately 6.0 × 5.5 cm. Contrast-enhanced ultrasound (CEUS) showed a cystic-solid lesion with honeycomb-like enhancement in the arterial phase, in which multiple disordered unreinforced tubular columnar areas were seen. No obvious papillary structure was found. The enhanced region was slowly cleared in the portal and delayed phases. Abdominal contrast-enhanced computed tomography (CT) scans (**Figure 1**) showed a honeycomb-like cystic-solid lesion with a tubulocystic manifestation lacking well-defined borders in S6 and no dilation of the major intrahepatic bile duct in the background liver. The cystic components were low-density and showed no enhancement in the arterial phase. The solid components, which were septa or the cystic wall, were more enhanced than the normal hepatic parenchyma in the arterial and portal phases and were consistent with normal hepatic parenchyma in the equilibrium phase. Abdominal magnetic resonance imaging (MRI) showed an irregular-shaped multicystic mass with a mixed signal shadow in S6. The lesion was revealed as an irregular tubular low-density area on T1-weighted images and a high-intensity area on T2-weighted images, which were interspersed with strips of slightly higher signal shadows. The signal of the solid component of the intermediate inclusion was not high on diffusion-weighted imaging (DWI), while the apparent diffusion coefficient (ADC) signal was high, indicating that the dispersion was not limited. The solid components of the lesion were enhanced in the late arterial phase by injecting the contrast medium, gadoxetic acid disodium. In the hepatobiliary phase, the whole lesion was low signal. The mass had no obvious invasion into adjacent structures and was thought to be benign. Magnetic resonance cholangiopancreatography (MRCP) showed intrahepatic hybrid-density cystic-solid masses that did not communicate with the bile duct. Intrahepatic and extrahepatic bile ducts were not dilated. No definite abnormal signal shadow was found in the bile duct cavity and gallbladder. Imaging examination did not reveal any bile duct stones (**Figure 2**). To exclude liver metastatic carcinoma caused by gastrointestinal malignancies, gastroscopy and colonoscopy were performed and no obvious abnormalities were detected. Duodenal papilla was normal, and no colloidal mucus was present. Based on these results, the lesion was suspected to be MCBH but other diseases such as HMH, VMC, Caroli's disease, biliary cystadenoma, and CHFC could not yet be excluded.

Since MCBH is a localized cystic-solid lesion, it can be difficult to diagnose by needle biopsy due to limited sampling of the lesion and heterogeneous distribution of the tumor components. After communicating with the patient and his relatives, surgical resection was performed. This was an open operation. The lesion could not be observed in the liver surface. The intraoperative ultrasonic testing was performed and the lesion was located in the right posterior segment VI of liver. Anatomical resection of segment VI was performed and the resection margin was more than 1 cm to the lesion. No enlarged lymph nodes were found during the operation. The residual liver had no tumors and showed healthy texture by intraoperative ultrasound. The operation was successful, lasting about 2 h, and the intraoperative bleeding was 100 ml.

The surgical specimen revealed an approximately 6.0 × 5.5 cm nodular mass. A cystic-solid lesion with a honeycomb appearance and gray-white, medium texture, was seen in a section of the resected specimen. The lesion was composed of diffuse, cystically dilated ductal structures that were

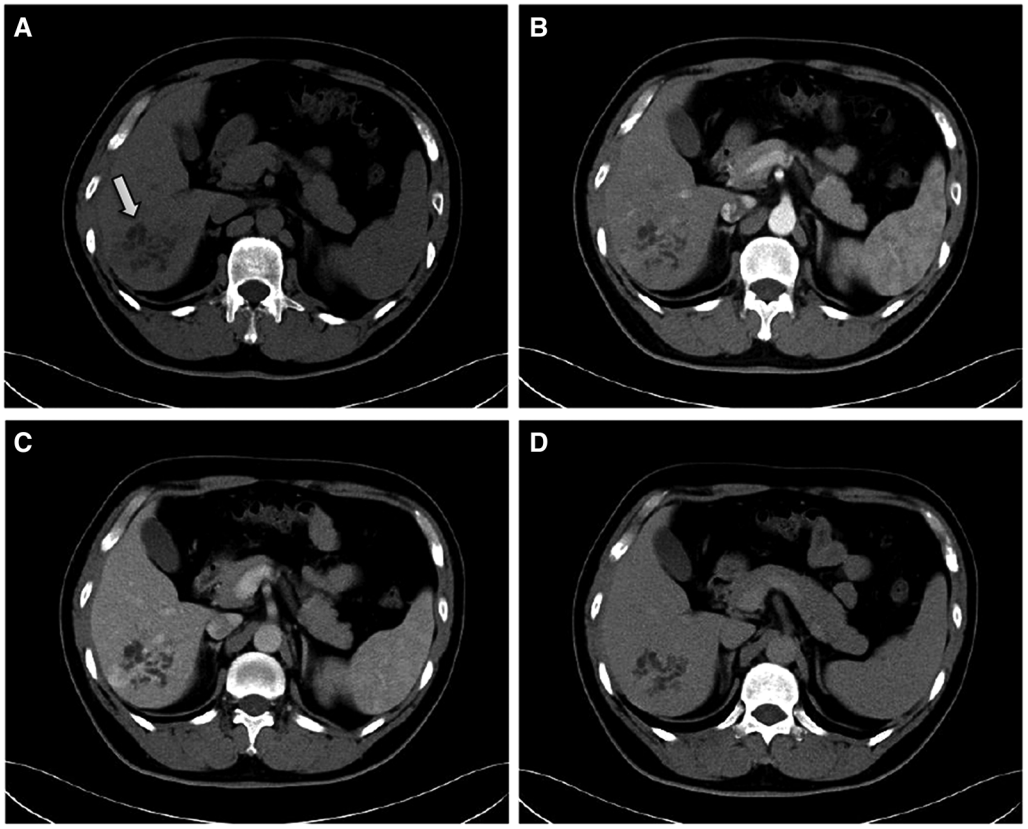

FIGURE 1
Contrast-enhanced CT findings. (A) plain scan, (B) arterial, (C) portal and (D) equilibrium phases, respectively. The CT scan shows a honeycomb-like cystic–solid lesion in segment 6 of the liver (white arrow). The cystic components show no enhancement during the arterial phase. The solid components are more enhanced compared with the normal hepatic parenchyma in the arterial and portal phases and are consistent with the normal hepatic parenchyma in the equilibrium phase.

approximately 0.1–1.5 cm in diameter and surrounded by fibrous tissue. The lesion was filled with clear, colorless liquid surrounded by normal liver tissue.

Low-power microscopy displayed a relative clearance boundary in the lesion area that consisted of ductal structures, periductal glands, fibrous connective tissues, and blood vessels. Ductal structures were cystically dilated and irregularly angulated. Bile-stained materials were observed in some ducts and the peripheral bile ducts were not dilated. High-power microscopy showed that the ductal epithelium was composed of a monolayered columnar and cuboidal epithelium that was morphologically identical to biliary epithelium. Fibrous connective tissue around the ducts contained only mild lymphocytic infiltration. Normal hepatocytes were observed between the cystic ducts. There were no smooth muscle elements or ovarian-like stroma, and there were no atypical cells or papillary growth of the epithelial cells. Synchronous biliary hamartomas, nodules, steatosis, or significant fibrosis were not observed in the non-lesion liver tissue. Immunohistochemistry showed CK7 and CK19 positivity in the dilated duct epithelium and CD34 positivity in the vessels. Ki-67 antigen staining revealed the proliferative activity of individual cells (**Figure 3**).

Final diagnosis

Based on the clinical manifestations, imaging and histological results, the final diagnosis was confirmed as MCBH. The patient recovered well after the operation and was discharged from the hospital. At 6 mo postoperatively, the patient was still alive.

Discussion

MCBH is a very rare hepatic benign neoplasm. It was first reported in 2005 (2) and described as a solitary cystic lesion of bile duct hamartoma. Zen et al. (3) proposed the concept of MCBH and described its characteristic pathological

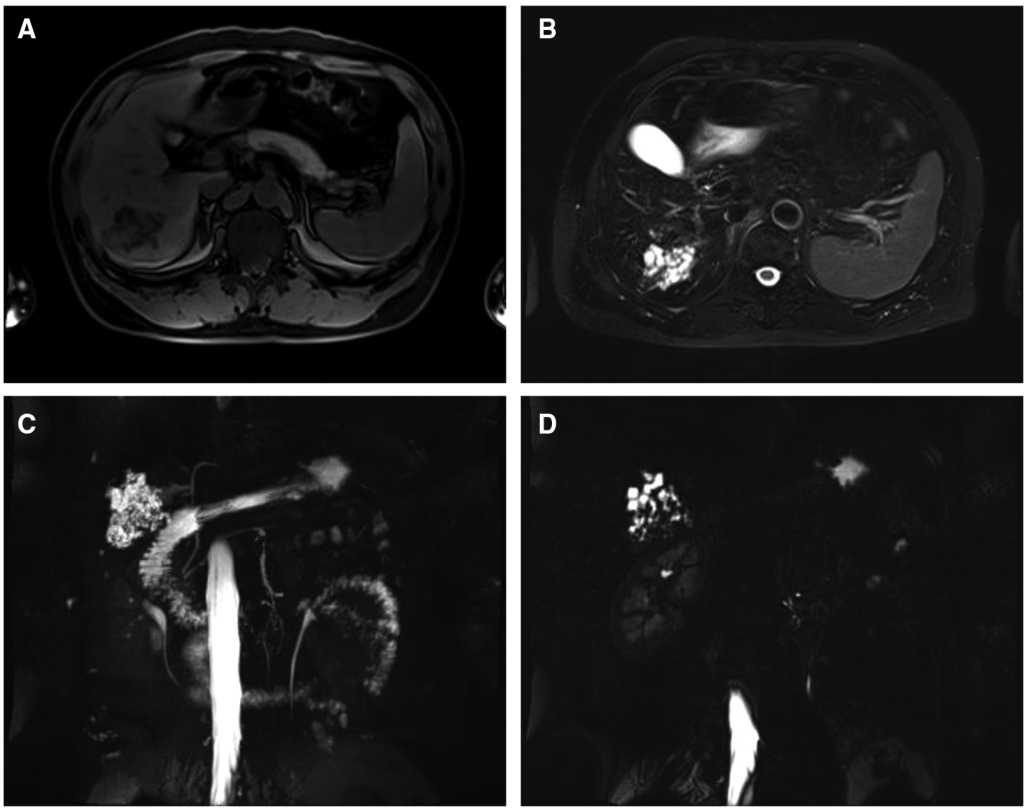

FIGURE 2
MRI findings of a lesion that is an irregular tubular (A) low-density area on T1 and (B) high-intensity area on T2. (C) and (D) MRCP findings of the mass that does not communicate with the bile duct. The intrahepatic and extrahepatic bile ducts are not dilated.

findings. Kai K et al. (4) reported a case with an intrahepatic lesion type, and suggested that the lesion occurred not only on the liver surface but also within the hepatic parenchyma. In 2010, Ryu Y et al. (1) first summarized the imaging features of MCBH. The lesion described in the current case report was near the liver surface but did not protrude outside. Based on Zen et al.'s standard and Ryu et al.'s imaging features, this lesion was diagnosed as MCBH. However, there were still several other diseases that needed to be ruled out, including HMH, VMC, Caroli's disease, Biliary cystadenoma, CHFC, and IPNB.

HMH is a large, well-circumscribed, multiloculated cystic mass (5) that can vary in size up to >30 cm. The cystic structures contain yellowish fluid with occasional gelatinous material (6). Most (80%) HMH patients are ≤2 years of age (7). Very few adult cases are reported, and female incidence is relatively higher. The patient described in the current study was a middle-aged man. He had a cystic-solid lesion without well-defined borders and had cystically dilated ductal structures measuring 0.1–1.5 cm in diameter that were filled with clear, colorless liquid. These findings, combined with the pathology, do not support a diagnosis of HMH.

VMC is characterized by discretely distributed, well-defined, cystically dilated bile ducts. Contrary to the relatively large size of nodules in MCBH, the nodules in VMC are small (<1.5 cm), usually between 0.2 and 0.5 cm in diameter. No enhancement is seen using enhanced CT/MRI (8). The current case was a focal lesion. The cystically dilated ductal structures were 0.1–1.5 cm and most were >0.5 cm. The solid components were enhanced using contrast agents. The current case did not support a VMC diagnosis, but further verification is needed to rule out the possibility that it is a VMC variant.

The typical imaging manifestation of Caroli's disease includes enlarged intrahepatic bile ducts that communicate with the bile duct system (9), and accompanied by a "central dot sign" (10). The lesions are not enhanced after contrast injection and are often accompanied by congenital hepatic fibrosis. The current case had no "central dot sign" and the solid components were enhanced in the arterial phase. The cystic dilatation tubes were not linked to the bile duct, and there was no hepatic fibrosis. Thus, Caroli's disease can be safely excluded.

Biliary cystadenoma is rarely encountered in males. The condition manifests as multiple septa in the large cyst

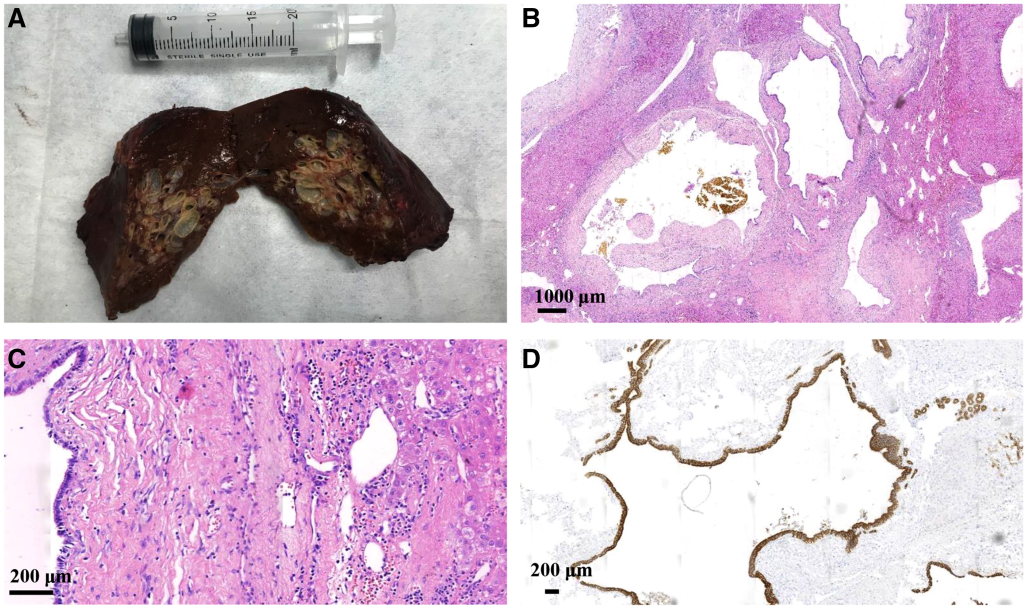

FIGURE 3
The surgical specimen (A) shows a nodular mass with a gray-white honeycomb-like cystic-solid lesion observed in one section. Hematoxylin and eosin staining under (B) low-power microscopy displaying cystically dilated ductal and irregularly angulated structures along with bile-stained materials observed in some ducts, and (C) high-power microscopy showing that the ductal epithelium is composed of monolayered columnar and cuboidal epithelium. Normal hepatocytes are observed between the cystic ducts. (D) Immunohistochemistry showing CK7 and CK19 positivity in the dilated duct epithelium.

which are divided into multiple small cysts of different sizes, usually with "ovarian-like" stroma. Imaging of the patient in the current case study revealed multiple tubular shadows twisted into a honeycomb-like lesion with solid components in the middle. There were clear differences in the imaging manifestations of these two diseases. In addition to the lack of "ovarian-like" stroma, the current case did not support biliary cystadenoma. CHFC has a unilocular cystic appearance and the presence of a four-layered cyst wall (11). A ciliated columnar epithelium is essential for the diagnosis of CHFC. Thus, this disease can be excluded.

IPNB is characterized by marked dilation or cystic lesions of the bile ducts with papillary structures (12) which are connected to the main hepatic duct, and the duodenal papilla is usually accompanied by colloidal mucus outflow. The current patient's liver function and tumor markers were normal, imaging did not reveal any papillary structures, and the lesions did not communicate with the biliary system. Gastroscopy revealed no colloidal mucus overflow from the duodenal papilla. Thus, this disease can also be excluded.

All published literature on MCBH were collected. Only 17 cases have been recorded in the literature to date, with the one described here being the eighteenth case (**Table 1**). MRI of the current case revealed that the DWI signal was not high while the ADC signal was high. There was no obvious invasion of adjacent structures, so the possibility of a malignant lesion was essentially ruled out. After reviewing all 18 case reports, the characteristics of MCBH are summarized as follows: (1) A neoplasm generally located near the liver surface and/or protruding from the liver; (2) A localized cystic–solid neoplasm with a honeycomb-like appearance without well-defined borders. The cystic components show no enhancement, while the solid components are enhanced in the arterial phase; (3) Intrahepatic and extrahepatic bile ducts are not dilated. The cystic dilatation tubes are not connected to the biliary system; (4) The neoplasm is composed of ductal structures, periductal glands, and fibrous connective tissues, and normal liver parenchyma intermingles within the nodular lesion; (5) The neoplasm contains bile-like materials within ducts; (6) Biliary-type CKs are positive on immunostaining. Given the patient's age, sex, previous disease history, blood test results, and 1–3 imaging characteristics, many diseases, including HMH, VMC, Caroli's disease, Biliary cystadenoma, and IPNB, could be excluded. However, a small number of diseases require diagnosis through pathology. The imaging features described here should help to narrow the scope of differential diagnosis and aid early identification and diagnosis of MCBH.

TABLE 1 Summary of cases with multicystic biliary hamartoma (MCBH).

Case No.	Ref.	Age (years)/Sex	Size (cm)	Location	protruding from the liver	Imaging or histological features
1	Kobayashi et al, 2005 (2)	30/M	3.6	Seg VI	No	Small cysts (<0.5 cm) and larger cysts (0.5–1.2 cm), lined by low columnar or cuboidal epithelium, contained bile-stained material, were embedded in a fibrous stroma
2	Zen et al, 2006 (3)	59/M	4.2	Seg VI	Yes	A relatively well-circumscribed nodule was enhanced on CT by contrast medium and sustained until the delayed phase. Histologic features included xanthogranulomatous inflammations, ductal structures, periductal glands, and fibrous connective tissues containing blood vessels. Some ducts contained bile-like brown materials with focal calcifications. Ductal epithelium diffusely expressed biliary-type CKs such as CK7 and CK19
3		70/F	1.8	Seg III	Yes	CT (arterial phase) displays multiple tiny cysts with thin walls and septae. Walls and septae are enhanced slightly. CT (equivalent phase) cyst walls and septae are more markedly enhanced than in arterial phase. CT during hepatic arteriography (CTHA) clearly shows enhanced area of the cysts wall and septae. Cut surface demonstrates honeycomb-like appearance
4		69/F	2.8	Seg III	Yes	A multilocular cystic lesion containing many small cystic spaces
5	Kai et al, 2008 (4)	55/M	5.0	Seg VI	No	CT imaging during arterial portography (CTAP) showed an intrahepatic, multicystic, honeycomb-like lesion with contrast enhancement in a part of the septum. A low density area on T1-weighted images and a multiple bulboid high intensity area on T2-weighted images. The bile ducts were not dilated in the background liver
6	Ryu et al, 2010 (1)	45/M	2.0–3.5 (cases no. 6-8)	Seg VII	No	MRI and CT scan showed normal liver parenchyma was intermingled around the lesion. Pathological findings demonstrated hepatic parenchyma was observed among ductal structures
7		58/M		Seg III	No	CT (immediately after endoscopic retrograde cholangiography) showed that contrast medium did not enter the lesion
8		55/F		Seg VI/VII	No	
9	Song et al, 2013 (13)	52/M	2.7	Seg III	No	On MRI, MCBHs are hypointense on T1-weighted imaging. T2-weighted imaging reveals a multicystic, honeycomb-like lesion with bright, high signal intensity. Histologically, the lesion consisted of multiple dilated cystic ducts lined by biliary type epithelial cells, periductal glands and connective tissue, which included small amounts of hepatic parenchyma and blood vessels
10	Beard et al, 2014 (14)	48/F	4.7	Seg VIII	No	The radiographic appearance is that of a peripherally located, tubulocystic, honeycomb-like mass, consistent with an aggregate of dilated biliary ducts and intermingled normal hepatic parenchyma. The more common occurrence at the periphery rather than centrally. Pathological findings included microscopic islands of hepatic parenchyma within fibrous tissue that were not just at the periphery, but also in the center of the lesion
11	Yoh et al, 2014 (15)	69/M	3.0	Seg III	No	The peripheral site of this lesion is slightly enhanced on the arterial phase. On the portal phase, the ring-enhancement of the lesion is clearer and shows honeycomb-like dilated bile duct
12	Fernández-Carrión et al, 2015 (16)	60/F	5.0	Seg VI	No	
13	Tominaga et al, 2015 (17)	26/M	10.0	Seg V/VI	Yes	MRCP revealed an intrahepatic cystic tumor which did not communicate with the main hepatic duct in the hilum. The left bile duct and the common hepatic duct were not dilated, and there was no communication with the main duct
14	Morinaga et al, 2017 (18)	53/M	12.0	left lobe of the liver	Yes	Positron-emission tomography (PET)-CT revealed no uptake of fluorodeoxyglucose in the lesion. On endoscopic retrograde cholangiopancreatography (ERCP), the multicystic lesion did not communicate with the main hepatic bile duct
15	Ogura et al, 2018 (19)	77/F	12.0	Seg III	Yes	No communication between the biliary tract and the lesion is evident under ERCP
16	Mu et al, 2021 (20)	37/M	7.7	Seg VI	No	
17	Wang et al, 2022 (21)	14/M	17.0	Seg III	No	
Present case		44/M	6.0	Seg VI	No	

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Conclusions

MCBH is a very rare hepatic benign neoplasm that is associated with a localized cystic-solid mass. The incidence and natural history of this disease remain unknown. In the absence of characteristic diagnostic imaging criteria, effective serological markers, or genetic detection, diagnosis is dependent on imaging combined with histology after surgical resection. In this case study, we summarize the imaging and histological features of this disease. Importantly, we focus on those imaging characteristics that aid the diagnosis of MCBH using non-invasive methods. Imaging results combined with neoplasm size and patient symptoms will facilitate clinicians in selecting surgery or follow-up for individual patients, thereby preventing the need to rely on simple surgical resection and consequently reducing pain and economic burden for patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JL: managed the case and conceived the study. YKY: analyzed and interpreted the data. YZ: performed the operation. GQL: performed the histopathological review. WJH: analyzed the imaging data. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Long-term outcomes of laparoscopic liver resection versus open liver resection for hepatocellular carcinoma: A single-center 10-year experience

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Background: Laparoscopic liver resection (LLR) for hepatocellular carcinoma (HCC) has increased. However, the long-term outcomes of LLR for HCCs should be validated further. Besides, the validity of laparoscopic minor liver resection in difficult segments (1, 4a, 7, 8) (LMLR-DS) and laparoscopic major hepatectomy (LMH) for HCCs need to be studied.

Methods: A total of 1773 HCC patients were collected: 683 received LLR and 1090 received OLR. Propensity score matching (PSM) with 1:1 ratio was used to eliminate the selection bias. Short-term and long-term outcomes were compared. In subgroup analyses, the validity of LMLR-DS or LMH for HCCs was studied.

Results: After PSM, 567 patients were in LLR or OLR group. LLR had lower intraoperative blood-loss and shorter postoperative hospital-stays than OLR. The postoperative complications were lower in LLR group (23.8% *vs.* 32.8%, P=0.001). The Overall survival (OS) and disease-free survival (DFS) had no significant difference between LLR and OLR groups (P=0.973, P=0.812). The cumulative 1-, 3-, and 5-year OR rates were 87.9%, 68.9%, and 57.7% for LLR group, and 85.9%, 68.8%, 58.8% for OLR group. The cumulative 1-, 3-, and 5-year DFS rates were 73.0%, 51.5%, 40.6% for LLR group, and 70.3%, 49.0%, 42.4% for OLR group. In subgroup analyses, 178 patients were in LMLR-DS or open surgery (OMLR-DS) group after PSM. LMLR-DS had lower intraoperative blood-loss and shorter postoperative hospital-stays than OMLR-DS. The postoperative complications were lower in LMLR-DS group. The OS and DFS had no difference between LMLR-DS and OMLR-DS groups. The cumulative 5-year OR and DFS rates were 61.6%, 43.9% for LMLR-DS group, and 66.5%, 47.7% for OMLR-DS group. In another subgroup analyses, 115 patients were in LMH or open major hepatectomy (OMH) group. LMH had lower blood-loss and shorter postoperative hospital-stays than OMH. The complications, OS and DFS had no significantly differences between two groups. The cumulative 5-year OR and DFS rates were 44.3%, 29.9% for LMH group, and 44.7%, 33.2% for OMH group.

Conclusions: LLR for HCCs showed better short-term outcomes and comparable long-term outcomes with OLR, even for patients who received LMLR-DS or LMH. LLR could be reliable and recommended for HCC treatment.

KEYWORDS

hepatocellar carcinoma, laparoscopic liver resection, open liver resection, laparoscopic minor liver resection in difficult segments, laparoscopic major hepatectomy, prognosis

Introduction

The Global Cancer Statistics 2020 reports that primary liver cancer is the sixth common malignancy and the third leading cause of tumor-related death (1). Hepatocellular carcinoma (HCC), which accounts for 75-85% of primary liver cancer, is a global health challenge (1, 2). Liver resection (LR) remains the mainstay of curative treatment for HCC (3, 4). LR mainly includes two types: open liver resection (OLR) and laparoscopic liver resection (LLR). OLR is the traditional and standard procedure for HCC treatment. With the development of laparoscopic technique and equipment, LLR has been progressively increasing in recent years (5–7).

Clinical researches of LLR for HCCs have always been the hot area worldwide. Advantages of LLR are reported with regard to improved short-term outcomes compared with OLR (8). However, the long-term outcome of LLR for HCCs has become an important topic of debate (9–12). Although several recent studies show that LLR has similar long-term outcomes with OLR for HCCs (13–16), it needs to be validated further in more studies with a larger number of cases. Moreover, according to Asia Pacific Consensus and Southampton Consensus Guidelines (6, 7), laparoscopic minor liver resections (LMLR) in anterolateral segments (2, 3, 4b, 5, 6), is reliable and recommended for HCC treatment, but on the other hand, laparoscopic minor liver resection in difficult segments (1, 4a, 7, 8) (LMLR-DS) and laparoscopic major hepatectomy (LMH) for HCC treatment needs to be investigated further.

The aim of this study was to compare the short-term and long-term outcomes of LLR with those of OLR for HCC in well-matched patient groups using propensity score matching (PSM) with a large number of cases at a single center. Moreover, the outcomes of LMLR-DS and LMH for HCCs were studied in subgroup analyses.

Methods

Study design and patients

We retrospectively reviewed the data for patients who received LR for HCC in Southwest hospital, Army medical university, Chongqing, China from January 2009 to December 2017.The inclusion criteria was as follows: (1) patients aged 18-75 years; (2) liver function classified as Child-Pugh A or B; (3) the remaining liver volume was adequate with the preoperative evaluation; (4) histopathological confirmation of HCC; and (5) no extrahepatic metastasis. The exclusion criteria were as follows: (1) patients with recurrent HCC; (2) liver resection combined with abdominal organ resection other than gallbladder resection; and (3) patients with HCC who underwent prior RFA or TACE.

A total of 1773 patients with HCC were collected in this study: 683 patients in LLR group and 1090 patients in OLR group (Supplementary Table S1). Preoperative evaluations were similar in two groups and included routine blood tests, liver function, coagulation examinations, serum tumor markers, indocyanine green retention test at 15 minutes (ICG-R15), and triphasic enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI). Routine blood and hepatic function tests were performed after surgery. Abdominal ultrasonography was routinely conducted for patients before discharge. LMLR (≤ 2 segments) or LMH (≥ 3 contiguous segments) were defined according to the previous study (8).The severity of postoperative complications was graded by the Clavien–Dindo classification, and the severe complications were defned as Clavien–Dindo grade III and above (17). This study was approved by the Ethics Committee of Southwest Hospital of Army Medical University.

Surgical procedure

For LLR, either 3D or 2D laparoscopic system was used. The patient was placed in the supine position. Carbon dioxide pneumoperitoneum was established with a pressure of 11–13 mmHg. Two 12 mm ports and two 5 mm ports were applied for the operation, and one 12mm port was used for the laparoscope. Laparoscopic ultrasonography was routinely performed to confirm the positions of tumors and guide the dissection line. The Pringle maneuver was applied to control blood loss. The liver parenchyma was dissected using the ultrasonic dissector. Intraparenchymal vascular and biliary structures (≥3 mm) were ligated by titanium clips or Hem-o-lock clips. The main Glissonian pedicles or hepatic veins were transected by the laparoscopic linear stapler or Hem-o-lock clips after ligation. The specimen was placed into a sterile bag and extracted through a suprapubic incision or an upper abdominal midline incision.

For OLR, a reverse L-incision or right subcostal incision was conducted. The operating procedure was similar to LLR. CUSA or clamp crushing was used as the main method for liver parenchyma dissection.

Follow-up

The follow-up was conducted every one month within three months after operation, and then every three months within two years and three or six months afterwards. Routine investigations at each follow-up included routine blood tests, liver function, tumor markers, abdominal ultrasonography, and even CT or MRI if necessary. Overall survival (OS) was defined as the time from the surgery date to death from any cause or the last follow-up. Disease free survival (DFS) was defined as the time from the surgery date to tumor recurrence. All patients were followed up with the same protocol.

Statistical analysis

PSM with 1:1 ratio was used to eliminate the selection bias between LLR and OLR groups based on the nearest neighbor matching method without replacement. The propensity score covariates in this study included age, gender, HBV, HCV, liver cirrhosis, Child–Pugh score, American Society of Anesthesiologists score (ASA score), preoperative blood tests (ALT, TBIL, ALB, PT, Platelet count and AFP), ICG-R15, tumor location, tumor number, largest tumor diameter, type of LR, range of LR, resection tumor margin, margin status, histological grade, satellite nodule, portal vein invasion, bile duct invasion and TNM stage (Table 1). After matching, P values for the group samples were all greater than 0.05, indicating a good balance. Continuous variables were compared using a t test or Mann–Whitney test. Categorical variables were compared using the χ^2 or Fisher exact test. A two-tailed P value <0.05 was considered significant. Survival curves were estimated by the Kaplan-Meier method for OS and DFS, the log-rank test was used for between-group comparisons. P values < 0.05 were considered significant. All statistical analyses were performed using SPSS software version 25.0 (IBM SPSS Inc. Chicago, IL).

Results

Baseline characteristics

A total of 1773 patients with HCC were collected in this study, 683 patients received LLR and 1090 patients received OLR. The baseline characteristics were shown in Table 1. Between LLR and OLR groups, age, HBV-DNA and ASA scores were significantly different. Besides, the preoperative serum levels of TBIL, ALT, PT, Platelet count and AFP were different. Among the operative characteristics, tumor location, largest tumor diameters and the range of LR were significantly different between two groups. The characteristics of histological grade and portal vein invasion were also significantly different. Moreover, the TNM stage was different between two groups. After PSM with 1:1 ratio, there were 567 patients in each group with well-balanced baseline characteristics (Table 1).

Short-term outcomes

Short-term outcomes were compared between LLR and OLR groups after PSM (Table 2). The operative time was similar between two groups. On the other hand, the operative blood loss and the rate of blood transfusion in LLR groups were significantly lower than them in OLR group (200.00 ml *vs.* 300.00 ml, P<0.001; 8.6% *vs.* 12.3%, P=0.042). The perioperative mortality was similar between two groups. However, the overall postoperative complications in LLR group were significantly lower than them in OLR group (23.8% *vs.* 32.8%, P=0.001). The complications mainly included seroperitoneum, hydrothorax, infection, hemorrhage, bile leak, liver failure, respiratory failure and renal failure. Moreover, the severe complications (Clavien–Dindo grade III and above) were also significantly lower in LLR groups (5.1% *vs.* 8.6%, P=0.019). Besides, the postoperative hospital stays were significantly shorter in LLR group (10.00 days *vs.* 13.00 days, P<0.001). Together, the results showed that patients in LLR group had better short-term outcomes compared with them in OLR group.

Long-term outcomes

The long-term outcomes were compared between LLR and OLR groups after PSM. The OS and DFS curves were presented in Figure 1. Survival analysis showed that the OS had no significant difference between LLR and OLR groups (Figure 1, P=0.973). The cumulative 1-, 3-, and 5-year OS rates were 87.9%, 68.9%, and 57.7% for patients in LLR group, and were 85.9%, 68.8%, and 58.8% for patients in OLR group, respectively. Consistently, the DFS had no difference between LLR and OLR groups (Figure 1, P=0.812). The cumulative 1-, 3-, and 5-year DFS rates were 73.0%, 51.5%, and 40.6% for patients in LLR group, and were 70.3%, 49.0%, and 42.4% for patients in OLR group, respectively. Together, the results showed that patients in LLR group had comparable long-term outcomes with them in OLR group.

Subgroup analysis: LMLR-DS versus open minor liver resection in difficult segments (1, 4a, 7 and 8) (OMLR-DS) for HCCs

A subgroup analysis was performed to assess the outcomes of LMLR-DS for HCCs compared with OMLR-DS. After PSM with 1:1 ratio, there were 178 patients in LMLR-DS or OMLR-DS group, and all baseline characteristics were well-balanced (Supplementary Table S2). The operative time and the rate of blood transfusion were similar in two groups. While, the operative blood loss in LMLR-DS group was significantly lower than it in OMLR-DS group (200.00 ml *vs.* 300.00 ml, P<0.001). There was no perioperative death in both two groups. However, the overall and severe postoperative complications were significantly lower in LMLR-DS group compared with them in OMLR-DS group (27.5% *vs.* 39.9%, P=0.014; 3.9% *vs.* 11.2%, P=0.009; Table 3). The postoperative stays were significantly shorter in LMLR-DS group (10.00 days *vs.* 13.50 days, P<0.001). For long-term survival analysis, the OS had no significant difference between LMLR-DS and OMLR-DS groups (P=0.476, Figure 2). The cumulative 1-, 3-, and 5-year OS rates were 92.6%, 76.0%, and 61.6% for patients in LMLR-DS group, and were 90.9%, 78.2%, and 66.5% for patients in OMLR-DS group, respectively. Consistently, the DFS had no difference between LMLR-DS and OMLR-DS groups (Figure 2, P=0.536). The cumulative 1-, 3-, and 5-year DFS rates were 76.7%, 51.2%, and

TABLE 1 Baseline patient characteristics between laparoscopic liver resection (LLR) and open liver resection (OLR) groups.

Characteristics	Before PSM			After PSM		
	LLR (N=683)	OLR (N=1090)	P	LLR (N=567)	OLR (N=567)	P
Age	51.00 (45.00-60.00)	48.00 (42.00-57.00)	<0.001*	50.00 (44.00-59.00)	50.00 (44.00-60.00)	0.643
Gender			0.245			0.135
Male	586 (85.8%)	956 (87.7%)		484 (85.4%)	501 (88.4%)	
Female	97 (14.2%)	134 (12.3%)		83 (14.6%)	66 (11.6%)	
Positive HBV-DNA	587 (85.9%)	980 (89.9%)	0.011*	495 (87.3%)	502 (88.5%)	0.524
Positive HCV-RNA	8 (1.2%)	10 (0.9%)	0.604	6 (1.1%)	4 (0.7%)	0.525
Liver cirrhosis	449 (65.7%)	717 (65.8%)	0.986	379 (66.8%)	382 (67.4%)	0.850
Child-Pugh score			0.060			1.000
A	682 (99.9%)	1080 (99.1%)		566 (99.8%)	566 (99.8%)	
B	1 (0.1%)	10 (0.9%)		1 (0.2%)	1 (0.2%)	
ASA score			0.023*			0.953
I	372 (54.5%)	533 (48.9%)		302 (53.3%)	301 (53.1%)	
II	311 (45.5%)	557 (51.1%))		265 (46.7%)	266 (46.9%)	
TBIL(μmol/L)	15.20 (11.70-19.10)	16.10 (12.70-20.10)	<0.001*	15.30 (11.70-19.00)	15.30 (12.20-19.50)	0.268
ALT (IU/L)	34.00 (24.00-48.00)	38.00 (27.00-55.00)	<0.001*	35.00 (24.70-50.20)	36.00 (25.90-51.00)	0.409
ALB	42.70 (39.60-45.10)	42.90 (39.70-45.70)	0.105	42.80 (39.70-45.10)	42.90 (39.60-45.60)	0.620
PT (INR)	1.01 (0.97-1.06)	1.02 (0.98-1.08)	<0.001*	1.02 (0.97-1.06)	1.01 (0.97-1.06)	0.214
Platelet count (*103/μL)	134.00 (96.00-172.00)	144.00 (106.75-195.00)	<0.001*	134.00 (96.00-173.00)	134.00 (102.00-176.00)	0.294
AFP (≥400 ng/mL)	186 (27.2%)	433 (39.7%)	<0.001*	174 (30.7%)	171 (30.2%)	0.846
ICG-R15 (%)	4.40 (2.70-6.90)	4.50 (2.60-7.20)	0.465	4.50 (2.70-7.00)	4.40 (2.50-6.80)	0.623
Tumor Location			0.011*			0.754
Difficult segments (1, 4a, 7, 8)	205 (30.0%)	391 (35.9%)		195 (34.4%)	190 (33.5%)	
Simple segments (2, 3, 4b, 5, 6)	478 (70.0%)	699 (64.1%)		372 (65.6%)	377 (66.5%)	
Tumor number			0.712			0.767
1	637 (93.3%)	1006 (92.3%)		524 (92.4%)	520 (91.7%)	
2-3	42 (6.1%)	78 (7.1%)		39 (6.9%)	44 (7.8%)	
≥4	4 (0.6%)	6 (0.6%)		4 (0.7%)	3 (0.5%)	
Largest tumor diameters			<0.001*			0.892
≤5cm	535 (78.3%)	553 (50.7%)		419 (73.9%)	421 (74.3%)	
>5cm	148 (21.7%)	537 (49.3%)		148 (26.1%)	146 (25.7%)	
Type of LR			0.272			0.905
Anatomical LR	319 (46.7%)	480 (44.0%)		255 (45.0%)	257 (45.3%)	
Non-anatomical LR	364 (53.3%)	610 (56.0%)		312 (55.0%)	310 (54.7%)	

(Continued)

TABLE 1 Continued

Characteristics	Before PSM			After PSM		
	LLR (N=683)	OLR (N=1090)	P	LLR (N=567)	OLR (N=567)	P
Range of LR			<0.001*			0.717
Major	124 (18.2%)	380 (34.9%)		119 (21.0%)	124 (21.9%)	
Minor	559 (81.8%)	710 (65.1%)		448 (79.0%)	443 (78.1%)	
Resection tumor margin			0.054			0.307
≥1cm	658 (96.3%)	1028 (94.3%)		546 (96.3%)	539 (95.1%)	
<1cm	25 (3.7%)	62 (5.7%)		21 (3.7%)	28 (4.9%)	
Margin status			0.260			1.000
Negative	682 (99.9%)	1084 (99.4%)		566 (99.8%)	566 (99.8%)	
Positive	1 (0.1%)	6 (0.6%)		1 (0.2%)	1 (0.2%)	
Histological grade			<0.001*			0.077
Low	86 (12.6%)	219 (20.1%)		72 (12.7%)	96 (16.9%)	
Moderate	546 (79.9%)	811 (74.4%)		459 (81.0%)	428 (75.5%)	
High	51 (7.5%)	60 (5.5%)		36 (6.3%)	43 (7.6%)	
Satellite nodule			<0.001*			0.463
Positive	7 (1.0%)	42 (3.9%)		7 (1.2%)	10 (1.8%)	
Negative	676 (99.0%)	1048 (96.1%)		560 (98.8%)	557 (98.2%)	
Portal vein invasion			<0.001*			0.316
Positive	22 (3.2%)	136 (12.5%)		22 (3.9%)	29 (5.1%)	
Negative	661 (96.8%)	954 (87.5%)		545 (96.1%)	538 (94.9%)	
Bile duct invasion			0.655			1.000
Positive	1 (0.1%)	4 (0.4%)		1 (0.2%)	1 (0.2%)	
Negative	682 (99.9%)	1086 (99.6%)		566 (99.8%)	566 (99.8%)	
TNM stage			<0.001*			0.359
I-II	646 (94.6%)	918 (84.2%)		530 (93.5%)	522 (92.1%)	
III-IV	37 (5.4%)	172 (15.8%)		37 (6.5%)	45 (7.9%)	

HBV, hepatitis B virus; HCV, hepatitis C virus; ASA American Society of Anesthesiologists;TBIL, total bilirubin; ALT, alanine transaminase; PT, prothrombin time; AFP,alpha-fetoprotein; ICG-R15, indocyanine green retention test at 15 minutes. *P < 0.05.
(*P < 0.05, statistical significance).

43.9% for patients in LMLR-DS group, and were 75.7%, 54.1%, and 47.7% for patients in OMLR-DS group, respectively. Together, the results showed that LMLR-DS showed better short-term outcomes and similar long-term outocomes with OMLR-DS for HCCs.

Subgroup analysis: LMH versus open major hepatectomy (OMH) for HCCs

Another subgroup analysis was performed to assess short-term and long-term outcomes of LMH for HCCs compared with OMH. There were 115 patients in either LMH or OMH group after PSM, and all baseline characteristics were well-balanced (Supplementary Table S3). The operative time was similar in two groups. However, the operative blood loss and the rate of blood transfusion in LMH group were significantly lower than them in OMH group (300.00ml *vs.* 400.00ml, P=0.003; 13.0% *vs.* 24.3%, P=0.028; Table 4). There was no perioperative death in both two groups. Besides, the overall and severe postoperative complications had no significant difference between two groups (Table 4). The postoperative hospital stays were significantly shorter in LMH group (11.00 days *vs.* 14.00 days, P<0.001). For long-term survival analyses, the OS had no significant difference between LMH and OMH groups (P=0.939, Figure 3). The cumulative 1-, 3-, and 5-year OS rates were 70.8%, 53.9%, and 44.3% for patients in LMH group, and were 75.5%, 49.2%, and 44.7% for patients in OMH group, respectively. Consistently, the DFS had no difference between two groups (P=0.681, Figure 3). The cumulative 1-, 3-, and 5-year DFS rates were 54.4%, 42.2%, and 29.9% for patients in LMH group, and were 55.7%, 33.5%, and 33.2% for patients in OMH group, respectively. Together, the results showed

TABLE 2 Operative details and postoperative outcomes between laparoscopic liver resection (LLR) and open liver resection (OLR) groups after propensity score matching.

	LLR (N=567)	OLR (N=567)	P
Operative time (min)	205.00 (150.00-267.00)	200.00 (160.00-250.00)	0.652
Blood loss (ml)	200.00 (150.00-400.00)	300.00 (200.00-400.00)	<0.001*
Blood transfusion	49 (8.6%)	70 (12.3%)	0.042*
Perioperative mortality	0 (0%)	0 (0%)	1.000
Overall complications	135 (23.8%)	186 (32.8%)	0.001*
Seroperitoneum	55 (9.7%)	73 (12.9%)	
Hydrothorax	37 (6.5%)	47 (8.3%)	
Infection	25 (4.4%)	35 (6.2%)	
Hemorrhage	24 (4.2%)	51 (9.0%)	
Bile leak	3 (0.5%)	7 (1.2%)	
Liver failure	2 (0.4%)	4 (0.7%)	
Respiratory failure	1 (0.2%)	4 (0.7%)	
Renal Failure	0 (0.0%)	1 (0.2%)	
Severe complications (Clavien–Dindo III -IV)	29 (5.1%)	49 (8.6%)	0.019*
Postoperative hospital stay (D)	10.00 (8.00-12.00)	13.00 (11.00-15.00)	<0.001*

(*P < 0.05, statistical significance).

that LHM for HCCs had comparable short-term and long-term outcomes with OHM.

Discussion

As a minimally invasive technique, the application of LLR has increased rapidly. Initially, LMLR was mainly applied for HCCs located in anterolateral segments (18, 19). With the development of laparoscopic equipment and techniques, LMLR was gradually applied in difficult segments and LMH were also gradually applied for HCCs. However, the oncological adequacy of LLR for HCCs, especially LMLR-DS and LMH, has become an important topic of debate. Although several reports of the successful outcomes of LMLR-DS and LMH for HCCs have been published (20–23), most of them were performed with small number of cases, and the long-term outcomes were not available in most studies. Our present study included a large number of HCC patients who received LLR. The data of a relative long follow-up period were also included. Besides, we employed PSM to decrease the inter-group baseline differences. Moreover, subgroup

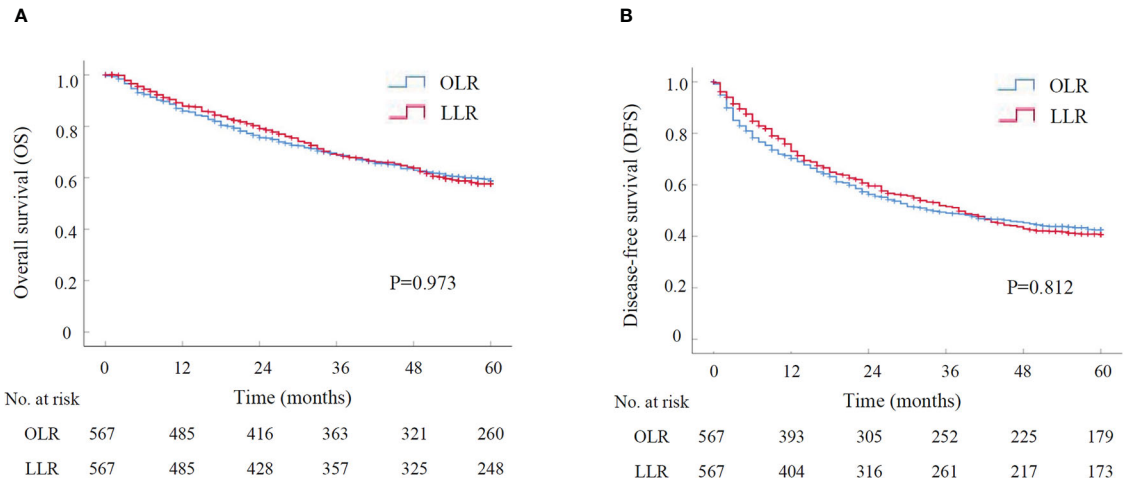

FIGURE 1
The survival curve of LLR versus OLR for HCCs after PSM by Kaplan-Meier analysis (N=567 for each group). **(A)** Overall survival; **(B)** Disease-free survival. LLR, laparoscopic liver resection; OLR, open liver resection; PSM, propensity score matching.

TABLE 3 Operative details and postoperative outcomes between laparoscopic minor liver resection in difficult segments (LMLR-DS) and open minor liver resection in difficult segments (OMLR-DS) groups after propensity score matching.

	LMLR-DS (N=178)	OMLR-DS (N=178)	P
Operative time (min)	202.50 (150.00-300.25)	204.50 (160.00-254.00)	0.961
Blood loss (ml)	200.00 (150.00-400.00)	300.00 (200.00-500.00)	<0.001*
Blood transfusion	17 (9.6%)	23 (12.9%)	0.314
Perioperative mortality	0 (0%)	0 (0%)	1.000
Overall complications	49 (27.5%)	71 (39.9%)	0.014*
Seroperitoneum	21 (11.8%)	30 (16.9%)	
Hydrothorax	16 (9.0%)	26 (14.6%)	
Infection	7 (3.9%)	9 (5.1%)	
Hemorrhage	7 (3.9%)	15 (8.4%)	
Bile leak	0 (0.0%)	2 (1.1%)	
Renal Failure	0 (0.0%)	1 (0.6%)	
Severe complications (Clavien–Dindo III -IV)	7 (3.9%)	20 (11.2%)	0.009*
Postoperative hospital stay (D)	10.00 (8.00-12.00)	13.50 (12.00-15.00)	<0.001*

(*P < 0.05, statistical significance).

analysis of either LMLR-DS or LMH for HCCs was performed, respectively. In these respects, our study was meaningful and convincing.

The Asia Pacific Consensus and Southampton Consensus Guidelines indicate that more evidence is needed to support the growth of LMLR-DS and LMH for HCCs (6, 7). One major problems of LMLR in segment 7 or 8 is the limited visualization (24), and several measures might be useful for overcoming this limitation in our experience: (1) the patient lied down with a cushion underneath the right back; (2) the right and cephalic sides of the operating table were raised; (3) the whole liver ligaments were separated and then the assistant pushed the right liver toward the left anterior inferior direction; (4) a water balloon was pulled under the right diaphragm to elevate the right posterosuperior segment. For LMLR in segment 1, the operative approach has always been an important issue. Three surgical approaches are described: left side, right side and trans-parenchymal approach (25, 26). Left side approach is commonly used for HCC in Spiegel's lobe. The most common approach for HCC in caudate process is from the right side. Our previous study showed that the trans-parenchymal approach might be suitable for selected HCC originating in the paracaval portion (27). Another major problem of LMLR-DS is the intraoperative bleeding. As the difficult segments (1, 4a, 7, 8) were close to the main hepatic veins, skilled suture techniques are necessary for control of hepatic vein bleeding. 3D laparoscopic system, which offers the surgeon binocular vision and depth perception, might be benefit for suture compared with 2D system

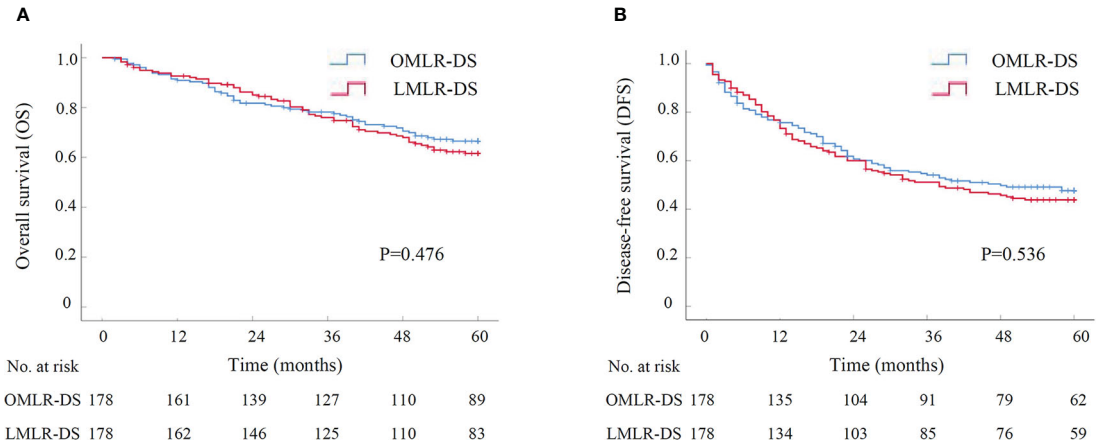

FIGURE 2
The survival curve of LMLR-DS versus OMLR-DS for HCCs after PSM by Kaplan-Meier analysis (N=178 for each group). **(A)** Overall survival; **(B)** Disease-free survival. LMLR-DS, laparoscopic minor liver resection in difficult segments (1, 4a, 7 and 8); OMLR-DS, open minor liver resection in difficult segments; PSM, propensity score matching.

TABLE 4 Operative details and postoperative outcomes between laparoscopic major hepatectomy (LMH) and open major hepatectomy (OMH) groups after propensity score matching.

	LMH (N=115)	OMH (N=115)	P
Operative time (min)	255.00 (204.00-321.00)	253.00 (203.00-315.00)	0.797
Blood loss (ml)	300.00 (200.00-500.00)	400.00 (300.00-600.00)	0.003*
Blood transfusion	15 (13.0%)	28 (24.3%)	0.028*
Perioperative mortality	0 (0%)	0 (0%)	1.000
Overall complications	34 (29.6%)	44 (38.3%)	0.164
Seroperitoneum	12 (10.4%)	14 (12.2%)	
Hydrothorax	10 (8.7%)	9 (7.8%)	
Hemorrhage	8 (7.0%)	17 (14.8%)	
Infection	4 (3.5%)	11 (9.6%)	
Bile leak	3 (2.6%)	2 (1.7%)	
Liver failure	2 (1.7%)	2 (1.7%)	
Respiratory failure	0 (0.0%)	1 (0.9%)	
Severe complications (Clavien–Dindo III -IV)	7 (6.1%)	12 (10.4%)	0.231
Postoperative hospital stay (D)	11.00 (9.00-13.00)	14.00 (12.00-17.00)	<0.001*

(*P < 0.05, statistical significance).

(28). Together, by using the above measures, LMLR-DS for HCCs could be successfully performed in most cases.

Most of the HCCs were combined with liver cirrhosis (29). LMH for HCCs is technically more demanding because of the increased risk of intraoperative bleeding and postoperative liver failure, especially in cirrhotic patients (22, 30). Some measures might be benefit for its performance in our experience. Firstly, Preoperative evaluation of liver function, Child-Pugh Grade A and ICG-R15 less than 10%, and remaining liver volume that accounts for >40% might be the prerequisites for HCC patients with liver cirrhosis to receive LMH (31, 32). Secondly, priority of Glissonian pedicle ligation could help to control the intraoperative bleeding (33), and Laennec's approach is a recently reported easy and reliable measure to isolate the Glissonean pedicles (34). The Laennec's approach might be more easily performed under the laparoscopic system because of the visual amplification compared with open surgery. Thirdly, the anterior approach of major hepatectomy, with benefit of reducing intraoperative bleeding compared with conventional approach, might be more easily performed under the laparoscopic system (35, 36). Fourthly, Pringle maneuver and low central venous pressure (LCVP, less than 5 cmH_2O) was used to reduce intraoperative bleeding (37–39). Through the above measures, LMH for HCCs, especially with liver cirrhosis, could be successfully performed in most cases.

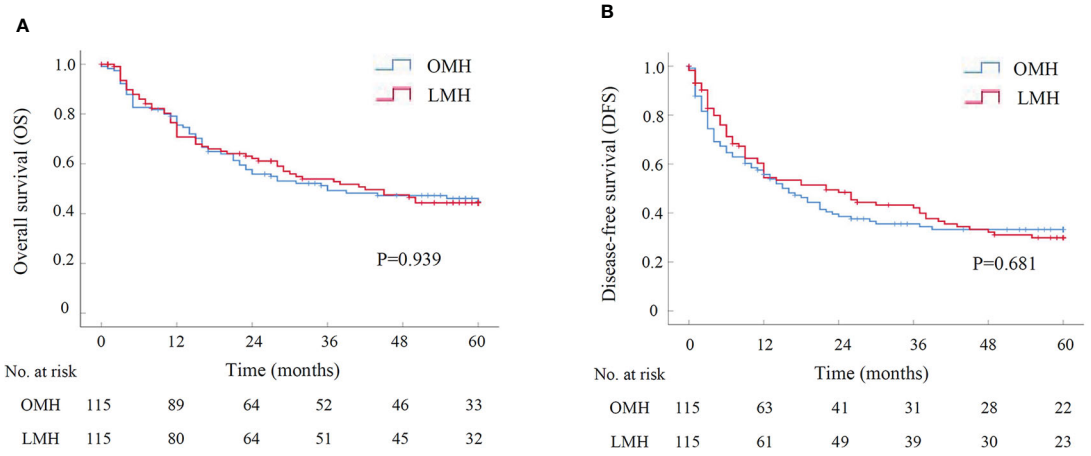

FIGURE 3
The survival curve of LMH versus OMH for HCCs after PSM by Kaplan-Meier analysis (N=115 for each group). **(A)** Overall survival; **(B)** Disease-free survival. LMH, laparoscopic major hepatectomy; OMH, open major hepatectomy; PSM, propensity score matching.

In our study, the short-term outcomes of LLR for HCCs were analyzed. In general, LLR had significantly less intraoperative blood loss and less blood transfusion compared with OLR. The control of hepatic vein bleeding is the major issue for LR. Although LCVP was performed in both LLR and OLR, the combination of LCVP and high pneumoperitoneum pressure (HPP, 13mmHg) might be more useful for control of hepatic vein bleeding in LLR. With the visual magnification of laparoscopic system, the parenchyma dissection in LLR might be more precise compared with it in OLR, which might be benefit for the decrease of intraoperative bleeding. Besides, the overall and severe postoperative complications after LLR were less than them after OLR. Because of the lower rate of complications, the postoperative hospital stays after LLR were shorter than it after OLR. Moreover, subgroup analyses confirmed that LMLR-DS had better short-term outcomes than OMLR-DS for HCCs. Patients after LHM also had lower operative blood loss and shorter postoperative hospital stays than OHM. Taken together, LLR could be a safe measure for HCC treatment.

The most important point of this study was to assess the long-term outcomes of LLR for HCCs. In general, LLR had comparable OS and DFS with OLR for HCCs. In subgroup analyses, LMLR-DS had similar OS and DFS with OMLR-DS for HCCs, and consistently, the OS and DFS had no differences between LMH and OMH groups. Taken together, considering that LLR had comparable long-term outcomes with OLR, LLR could be a reliable measure for HCC treatment. Thus, the indications of laparoscopic approach for HCCs in our center were mainly consistent with those of open approach. Besides, several points should be noticed for improving the long-term outcomes of either LLR or OLR for HCCs, which need to be validated further. Firstly, a wide-margin LR (≥1cm) might improve the long-term outcomes for patients with HCC (40, 41). Secondly, anatomic LR might be superior to non-anatomic LR regarding the long-term outcomes for HCCs (42, 43). Thirdly, the anterior approach for major hepatectomy with large HCC might have better long-term outcomes compared with the conventional approach (44).

Although our study included a large number of patients who received LLR for HCC, it still had limitations because that it was a retrospective study. Hence, a well-designed prospective study will be needed to affirm the validity of LLR for HCCs.

Conclusions

Our results indicated that LLR for HCCs showed better short-term outcomes and comparable long-term outcomes with OLR, even for patients who received LMLR in difficult segments (1, 4a, 7 and 8) or LMH. Thus, LLR could be reliable and recommended for HCC treatment.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Southwest Hospital of Army Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JL, SZ, FT, SL and JW participated in research design, data analysis, and writing of the manuscript. JC, YC, LC, XW and XL participated in data collection and analysis. All authors read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1112380/full#supplementary-material

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Adjuvant transarterial chemoembolization timing after radical resection is an independent prognostic factor for patients with hepatocellular carcinoma

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Background: It has been reported that postoperative adjuvant TACE (PA-TACE) treatment decreases recurrence and significantly improves the survival of patients who undergo radical resection of hepatocellular carcinoma (HCC) with high-risk recurrence factors. However, when to perform PA-TACE has not been fully studied.

Methods: We retrospectively collected the clinicopathologic characteristics of the patients with HCC between October 2013 and June 2020. The optimal cutoff value for PA-TACE time was determined based on the R package "maxstat". Logistic regression and Cox regression analysis were used to determine the effect of the choice of PA-TACE timing on prognosis.

Results: The analysis was performed on 789 patients with HCC, and 484 patients were finally involved and were divided into training cohort (378) and validation cohort (106). The PA-TACE timing was found to be associated with survival outcomes. Multivariate logistic analysis found independent predictors of the PA-TACE timing, including gender and history of HBV. Multivariate Cox analysis showed that Ki-67, tumor size, MVI and the PA-TACE timing were independent prognostic factors for RFS in HCC patients.

Conclusions: Based on this study, HCC patients with high-risk recurrence factors can receive personalized assistance in undergoing PA-TACE treatment and improve their survival outcomes.

KEYWORDS

HCC, TACE (transarterial chemoembolization), prognosis, timing, treatment

Highlights

This retrospective analysis was performed on 789 patients with high-risk recurrence factors who had undergone radical hepatectomy for HCC. 484 patients were finally entered into the analysis and were divided into training cohort (378) and validation cohort (106). With the results of this study, the PA-TACE timing after radical resection is an independent prognostic factor for patients with HCC. HCC patients with high-risk recurrence factors can receive personalized assistance in undergoing PA-TACE treatment and improve their survival outcomes.

Introduction

On a global scale, liver cancer is the fourth most common cause of cancer-related death and ranks sixth in terms of incidence (1). The most prevalent type of liver cancer, hepatocellular carcinoma (HCC), accounts for approximately 90% of all cases (2). There are curative treatments available for HCC patients, including resection, transplantation and ablation (3, 4). For most HCC cases, resection is the primary therapeutic option (4, 5). Despite this, tumor recurrence following hepatectomy remains a major hurdle in managing HCC effectively, with the 5-year recurrence rates reaching 60%-70% (6, 7). The conventional risk factors for recurrence include nonanatomical resection, tumor size, microvascular invasion (MVI), serum alpha-fetoprotein level (AFP) and multiple tumors (8–10). To improve the long-term prognosis of postoperative HCC, postoperative adjuvant treatments are urgently needed.

A variety of strategies employing adjuvant therapeutic modalities (both systemic and locoregional) have been proposed over the years, including transarterial chemoembolization (TACE), interferon (11), capecitabine (12), hepatic arterial infusion chemotherapy (13), sorafenib (14), immunotherapy and heparanase inhibitor PI-88 (15, 16), which have been proposed with varying degrees of success. When HCC is at an intermediate stage (BCLC), TACE is the first-line treatment recommended by the Barcelona Clinic Liver Cancer (BCLC) staging system. Meanwhile, TACE is regarded as a critical adjuvant therapy after radical resection in cases of HCC with high-risk recurrence factors to prevent recurrence. The effectiveness of postoperative adjuvant TACE (PA-TACE) in preventing recurrence and improving the prognosis of HCC has been established by a large number of studies (17–19). However, when to perform PA-TACE following radical hepatectomy and the factors affecting the PA-TACE timing have not been fully studied.

A retrospective analysis was conducted of the PA-TACE time, clinicopathological characteristics, and prognosis in HCC patients with high-risk recurrence factors. The recommended timing of PA-TACE was determined by using the optimal cutoff value method, and then the patients were divided into early and later TACE groups with significant prognostic differences. The potential factors affecting the PA-TACE timing were obtained by logistic regression analysis. Our final step was to incorporate the timing of PA-TACE into a multivariate Cox regression model and develop a prognostic nomogram to demonstrate that the PA-TACE timing was independently associated with the prognosis of HCC patients. Internal validation and comparison with conventional prognostic evaluation systems were also carried out. In our study, we assessed how the PA-TACE timing affects the prognosis of HCC patients, which provided recommendations for the PA-TACE timing after hepatectomy in HCC patients with high-risk recurrence factors and contributed to improving the prognosis of HCC.

Methods

Study population

We retrospectively identified consecutive patients with HCC who received radical hepatectomy as their primary therapy between October 2013 and June 2020 at the Affiliated Hospital of Qingdao University from our prospective database, and a diagnosis of HCC was confirmed by pathological reports. The inclusion criteria were as follows: (1) diagnosis of HCC by pathologic criteria; (2) >18 years and ≤80 years of age; (3) histopathologically confirmed HCC with a high risk of recurrence after resection and not receive targeted therapy and immunotherapy before recurrence.; (4) Child–Pugh classification A or B; (5) Eastern Cooperative Oncology Group performance score (ECOG PS) ≤2; and (6) R0 resection. The exclusion criteria were as follows: (1) preoperative treatment, such as TACE, radiofrequency ablation, and antineoplastic agents; (2) hepatectomy of recurrent HCC; (3) a history of other malignancies; (4) invaded macrovasculature, such as portal or hepatic veins, or extrahepatic metastasis; (5) incomplete follow-up data; and (6) intrahepatic recurrence before PA-TACE, which made PA-TACE impossible. The training cohort included 378 patients, and 244 were excluded. We set up a cohort of 167 patients from the Affiliated Hospital of Qingdao University between July 2019 and June 2020 as external validation. According to the inclusion criteria and exclusion criteria, 106 patients were included as the validation cohort. Table 1 summarized the demographic and pathological characteristics of HCC patients. Figure 1 shows the flow chart of the entire process.

Anonymized or confidential patient data were maintained, and patient privacy was protected. We followed the 1964 Helsinki Declaration and its later amendments or comparable ethical standards in all procedures. The Affiliated Hospital of Qingdao University Research Ethics Committee approved the study protocol, protocol code QYFY WZLL 27141.

Clinicopathologic characteristics and definitions

A variety of clinical information of patients was collected through preoperative imaging examinations (including abdominal B-ultrasound and contrast-enhanced computer tomography (CT) or magnetic resonance imaging (MRI)), laboratory examinations (including routine blood test, blood biochemical examination, coagulation tests, tumor marker examination and hepatitis serology tests), pathologic features, tumor recurrence, and details of the follow-up or date of death. Age, gender, body mass index (BMI), and history of HBV were included in the basic data collected from patients. We collected clinical characteristics, including alanine

TABLE 1 The demographic and pathological characteristics of the HCC patients.

	Training cohort (n=378)	Validation cohort (n=106)	P value
PA-TACE time (day)	41.03 (35.05,49.99)	41.91 (35.06,55.95)	0.646
TALT (40)	111 (29.37)	28 (26.42)	0.553
TAST (U/L)	25 (19,33.1)	23.55 (19.83,30)	0.479
TALB (g/L)	40.38 (36.74,46.15)	40.9 (36.65,47.7)	0.975
TTBIL (umol/L)	15.39 (12.2,20.71)	14.93 (11.87,19.7)	0.331
TAFP (ug/L)	6.09 (2.89,39.06)	5.92 (2.66,32.9)	0.817
TPT (t/s)	11.3 (10.4,12.3)	11.65 (10.6,12.7)	0.099
ALT (40)	146 (38.62)	36 (33.96)	0.381
AST (U/L)	29.15 (22.4,43)	28.1 (21,45.03)	0.810
ALB (g/L)	42.6 (38.79,48.47)	40.5 (37.6,49.3)	0.127
TBIL (umol/L)	16.9 (12.8,22.5)	16.07 (11.49,21.83)	0.484
AFP (20)	225 (59.52)	62 (58.49)	0.848
PT (t/s)	10.9 (10,11.73)	11.2 (10.1,11.9)	0.292
Ki-67	30 (20,50)	30 (20,40)	0.722
tumor size (cm)	4.2 (3,7)	5.1 (3.3,8)	0.219
tumor number	1 (1,1)	1 (1,1)	0.764
MVI	242 (64.02)	65 (61.32)	0.61
satellite lesions	54 (14.29)	18 (16.98)	0.491
high (cm)	1.7 (1.65,1.73)	1.7 (1.65,1.73)	0.456
weight (kg)	70 (62,76)	70 (64,80)	0.249
BMI	24.22 (22.02,26.35)	25.01 (22.84,27.02)	0.059
history of HBV	198 (52.38)	57 (53.77)	0.8
age	61 (54,68)	61 (55,67)	0.864
gender	311 (82.28)	90 (84.91)	0.525

PA-TACE, postoperative adjuvant TACE; ALT, alanine aminotransaminase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; AFP, serum alpha- fetoprotein; PT, prothrombin time; MVI, microvascular invasion; BMI, body mass index. The indicators before PA-TACE were displayed as "T + indicators", such as "TALT".

aminotransaminase (ALT), aspartate aminotransferase (AST), albumin (ALB), total bilirubin (TBIL), serum alpha-fetoprotein (AFP) and prothrombin time (PT), before surgery and PA-TACE. The indicators before PA-TACE were displayed as "T + indicators", such as "TALT". Since TALT, ALT and AFP are extremely skewed distribution, we converted TALT and ALT into binary variables with the upper limit of normal value of 40U/L, and AFP into binary variables with the boundary of 20ug/L (20, 21), and conduct subsequent analysis. Ki-67, tumor size, tumor number, microvascular invasion (MVI) and satellite lesions were confirmed based on imaging examinations and pathologic examination. PA-TACE time was defined as the number of days from hepatectomy to PA-TACE. The optimal cutoff value for PA-TACE time was obtained through the "survminer" package's surv_cutpoint() function of R software (22, 23). The clinicopathologic characteristics of the patients in training cohort are summarized in Table 2.

All specimens were sampled according to the "Evidence-based Practice Guidelines for Standardized Pathological Diagnosis of Primary Liver Cancer in China: 2015 Update" using a 7-point baseline sampling protocol (24). MVI is a condition in which tumor cells are visible on microscopy in a portal vein, hepatic vein, or large capsular vessel of the surrounding hepatic tissue (25). The maximum diameter of the pathology specimen was used to define tumor size. Tumor number was classified as 1, 2 and 3. The term satellite lesions refers to microscopic HCC nodules separated from the tumor by at least 2 cm of uninvolved liver parenchyma and not included in tumor counts. The surgical specimens were examined by two senior pathologists with more than 10 years of hepatic pathology experience. For discordant cases, consensus was reached through discussion.

Based on tumor characteristics identified by pathology reports, we evaluated the risk of recurrence for resection and included patients with high-risk recurrence factors. When a single tumor with MVI, two or three tumors, or a single tumor larger than 5 cm without MVI was present, patients were considered to have high-risk recurrence factors (8, 9, 18, 19).

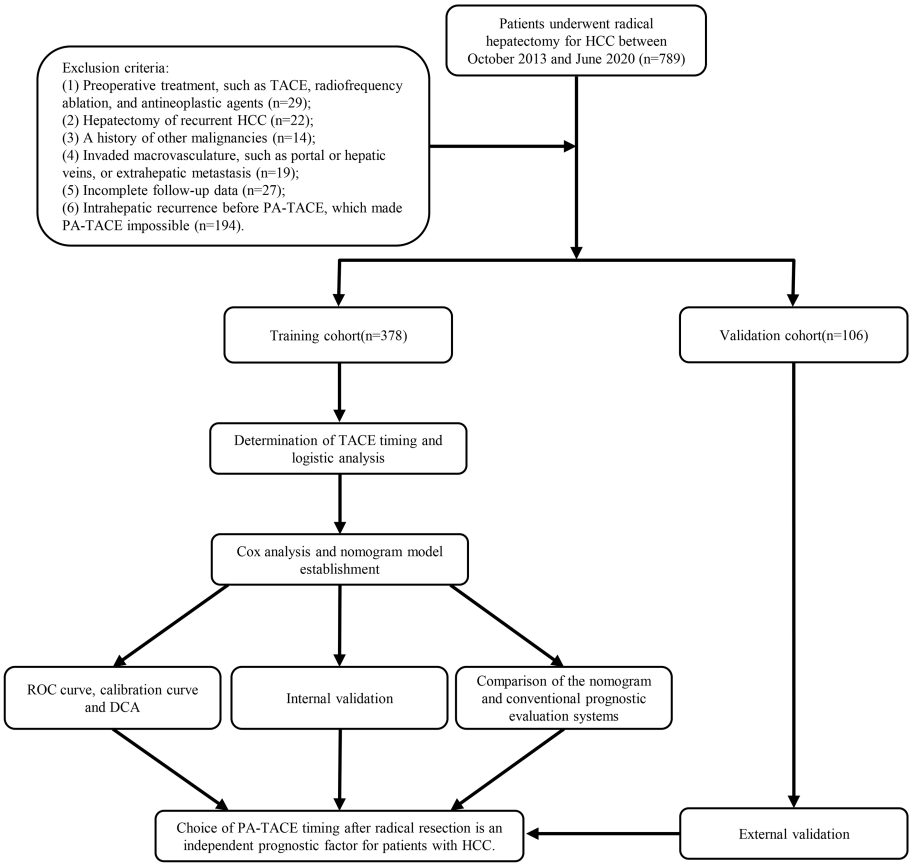

FIGURE 1
The flow chart of the study process.

Hepatectomy and TACE

Based on the Barcelona Clinic Liver Cancer (BCLC) staging system, we developed a treatment strategy for our patients. Child–Pugh classification and the indocyanine green (ICG) test were used to assess hepatectomy. Intraoperative sonography was used to determine the resection route. For inflow control of the liver during the operation, intermittent Pringle's maneuver (15 min of clamping followed by 5 min of release) was applied in selected cases. We used an ultrasonic dissector or a pean-clamp for the transection of the liver parenchyma. The histologic examination showed that all patients had achieved R0 resection, which was defined as no residual tumor and a negative margin.

For all patients, the liver function, serum AFP level and contrast-enhanced CT or MRI of the abdomen were evaluated approximately one month after surgery. Following the exclusion of patients who were not suitable for PA-TACE, those with high-risk recurrence factors were recommended to undergo PA-TACE. Socioeconomic status and compliance with doctors played a major role in whether patients followed physicians' recommendations. For this reason, we included patients up to 4 months after surgery in our study so we can study how the PA-TACE timing affected prognosis.

The Seldinger method was used to apply PA-TACE to the entire remnant liver. Any obvious tumor staining in the remnant liver was detected by hepatic angiography, computed tomography angiography, or both. An emulsion of lipiodol (5-10 mL) was applied after chemotherapeutic agents, including doxorubicin hydrochloride (10 mg), pirarubicin (THP), or pharmorubicin (20-40 mg), were administered slowly through the right and left hepatic arteries if tumor staining was not found. Based on body surface area and liver function, the dosage of lipiodol and doxorubicin was determined (26).

Suspicious imaging findings or biopsy-proven tumors were considered to be signs of recurrence (8). An evaluation of the therapeutic strategy was conducted once tumor recurrence was diagnosed based on tumor number, tumor location, liver function and general patient condition. Surgical reresection and ablation were used in the treatment with curative intent. The other treatment methods included TACE, targeted therapy, immunotherapy, etc.

Follow-up

Recurrence-free survival (RFS) was the primary endpoint of this study; overall survival (OS) and safety of PA-TACE were the secondary endpoints. In the first two years after surgery, patients were followed up once every 2 months and then once every 3 months thereafter. Each follow-up visit included liver function assessments, tumor markers, and abdominal ultrasounds. The patients were scheduled for contrast-enhanced CT or MRI once every 6 months or when recurrence/metastasis was suspected. RFS was defined as the time from the date of operation to the first

TABLE 2 The clinicopathologic characteristics of the HCC patients in training cohort.

Clinicopathologic characteristics	Total Patients	Early TACE group	Later TACE group	P value
RFS grouping	378	272	106	
gender	311 (82.28)	220 (80.88)	91 (85.85)	0.26
age (year)	61 (54,68)	60 (52.25,68)	64 (56.75,69)	0.03
PA-TACE time (day)	41.03 (35.05,49.99)	37.49 (33.93,41.99)	60.99 (52.94,75.06)	0.00
recurrence	232 (61.38)	157 (57.72)	75 (70.75)	0.02
RFS (year)	2.6 (0.75,3.64)	2.66 (0.85,3.70)	2.04 (0.55,3.60)	0.18
death	129 (34.13)	80 (29.41)	49 (46.23)	0.00
OS (year)	3.4 (2.62,5.03)	3.43 (2.66,5.03)	3.28 (2.29,5.04)	0.35
TALT (40)	111 (29.37)	91 (33.46)	20 (18.87)	0.01
TAST (U/L)	25 (19,33.1)	25.7 (19.03,33.30)	23.95 (17.9,32.98)	0.48
TALB (g/L)	40.38 (36.74,46.15)	40.3 (36.77,45.38)	41.1 (36.49,47.56)	0.40
TTBIL (umol/L)	15.39 (12.2,20.71)	15.2 (12.1,20.72)	15.94 (12.58,20.75)	0.53
TAFP (ug/L)	6.09 (2.89,39.06)	6.48 (2.98,42.56)	4.53 (2.48,33.41)	0.15
TPT (s)	11.3 (10.4,12.3)	11.3 (10.4,12.4)	11.25 (10.5,12.2)	0.56
ALT (40)	146 (38.62)	108 (39.71)	38 (35.85)	0.49
AST (U/L)	29.15 (22.4,43)	29.45 (22.27,42)	28.5 (22.38,43.3)	0.99
ALB (g/L)	42.6 (38.79,48.47)	42.66 (38.9,48.70)	42 (38.35,47.06)	0.31
TBIL (umol/L)	16.9 (12.8,22.50)	16.9 (13.1,22.28)	16.9 (11.96,22.73)	0.66
AFP (20)	225 (59.52)	162 (59.52)	63 (59.43)	0.98
PT (s)	10.9 (10,11.73)	10.9 (10.1,11.8)	10.8 (9.9,11.5)	0.24
Ki-67	30 (20,50)	30 (20,50)	30 (20,40)	0.75
tumor size (cm)	4.2 (3,7)	4.3 (2.85,7)	4.1 (3,7)	0.45
tumor number	1 (1,1)	1 (1,1)	1 (1,1)	0.35
MVI	242 (64.02)	185 (68.01)	57 (53.77)	0.01
satellite lesions	54 (14.29)	44 (16.18)	10 (9.43)	0.09
high (cm)	1.7 (1.65,1.73)	1.7 (1.65,1.74)	1.7 (1.65,1.73)	0.23
weight (kg)	70 (62,76)	70 (62,76)	69 (60,76.5)	0.35
BMI	24.22 (22.02,26.35)	24.24 (22.04,26.33)	23.88 (21.27,26.56)	0.58
history of HBV	198 (52.38)	127 (46.69)	71 (66.98)	0.00

RFS, disease free survival; OS, overall survival; PA-TACE, postoperative adjuvant TACE; ALT, alanine aminotransaminase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; AFP, serum alpha- fetoprotein; PT, prothrombin time; MVI, microvascular invasion; BMI, body mass index. The indicators before PA-TACE were displayed as "T + indicators", such as "TALT".

documented disease recurrence through independent radiological evaluation or liver biopsy, and or death by any cause, whichever occured first. OS was defined as the time from date of surgery to date of death regardless of the cause of death. We recorded adverse events (AEs) from the day of PA-TACE to the last day of follow-up. Using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, the safety of PA-TACE was evaluated (27). All follow-up data were summarized as of the end of January 2022.

External validation of the nomogram model was performed through the validation cohort. Exploratory subgroup analyses of RFS were performed in patients by age (≤65 years vs. >65 years), gender (male vs. female) and BMI (normal vs. abnormal).

Statistical analysis

SPSS software (version 25, IBM, New York, USA) was used for statistical analysis. The median (interquartile range) and the Mann –Whitney U test were performed for continuous variables with a skewed distribution, while the mean ± SD and t test were used for variables with a normal distribution. We compared categorical variables using the $\chi 2$ test or Fisher's exact test and presented them as frequencies and proportions. The Kaplan–Meier method was used to plot survival curves, and the log-rank test was used to compare them. Univariate logistic regression analysis was performed. Then, to evaluate the risk factors affecting the PA-

TACE timing, multivariate logistic regression analysis was conducted using the stepwise backward elimination procedure. The model fit was assessed with the Hosmer–Lemeshow goodness of fit test. Backward stepwise regression analysis was used to evaluate independent prognostic factors in univariate and multivariate Cox analyses.

We established a nomogram based on the results of multivariate Cox analysis using the package "rms" in R (version 4.1.2, Vienna, Austria). The receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) were used to quantify the discriminatory ability of the nomogram (28). With the Kaplan–Meier method, the calibration curve was depicted to assess whether the nomogram prediction was in agreement with observed real outcomes. Bootstraps with 1000 resamples were used for the validation of the nomogram and calibration curve construction. As described by Vickers and colleagues (29), the R package "rmda" was used to perform decision curve analysis (DCA) based on the net benefit, which was used to evaluate the performance of the established nomogram in clinical decision-making. The C-index was used for external validation, internal validation and comparison of the nomogram and conventional prognostic evaluation systems. Statistical significance was defined as a P value <0.05 for two-tailed tests.

Results

Prognostic value of the PA-TACE time

The optimal cutoff value of the PA-TACE time was determined to be 48.63 days for RFS (Figure 2A), to confirm the effect of the PA-TACE timing on prognosis. We then divided the patients into early and later TACE groups based on the optimal cutoff value. The Kaplan–Meier analysis showed that the PA-TACE timing was a significant poor prognostic factor for RFS (P<0.05) (Figure 2B).

Patients and clinicopathological characteristics

There was no significant difference in baseline characteristics between the training cohort and validation cohort (Table 1). A total of 789 HCC patients were treated at our center with radical (R0) partial hepatectomy. 484 qualified patients were enrolled in the final study and were divided into training cohort (378) and validation cohort (106). In training cohort: The median age of the patients was 61 (54-68) years, and 82.28% of them were male. The median time of PA-TACE was 41.03 (35.05-49.99) days. Postoperative pathologic examination confirmed that 242 (64.02%) patients had MVI, the median tumor diameter was 4.2 (3-7) cm, and 198 (52.38%) patients had HBV infection. As shown in Table 2, we divided the patients into early and later TACE groups based on the optimal cutoff value for RFS.

At the last follow-up in January 2022, the median RFS for all patients in training cohort was 2.6 (0.75-3.64) years, and the median OS was 3.4 (2.62-5.03) years. In the follow-up period, 232 (61.38%) patients relapsed, and 129 (34.13%) died, failing to reach the median survival. Compared to the late TACE group, the early TACE group had a significantly lower recurrence rate and mortality (57.72% vs. 70.75%, P<0.05; 29.41% vs. 46.23%, P<0.01). The RFS was 0.62 years longer in the early TACE group (2.66 years; 95% CI, 0.85-3.70 years) than in the later TACE group (2.04 years; 95% CI, 0.55-3.60 years). The OS was 0.15 years longer in the early TACE group (3.43 years; 95% CI, 2.66-5.03 years) than in the later TACE group (3.28 years; 95% CI, 2.29-5.04 years). The 1-, 3-, and 5-year RFS rates of the early TACE group were 72.1%, 48.8% and 37.7%, respectively; the 1-, 3-, and 5-year RFS rates of the later TACE group were 59.4%, 37.5% and 26.1%, respectively. In addition, the 1-, 3-, and 5-year OS rates of the early TACE group were 94.5%, 79.8% and 65.4%, respectively; the 1-, 3-, and 5-year OS rates of the later TACE group were 93.4%, 66.7% and 51.2%, respectively. In the validation cohort, the median RFS of HCC patients was 1.73 (0.93-2.07) years, and the median OS was 2.01 (1.71-2.22) years.

Risk factors related to the PA-TACE timing

Logistic regression analysis was conducted to identify risk factors associated with the PA-TACE timing. Regarding RFS, univariate logistic regression analysis revealed that TALT, ALT, AFP, MVI, satellite lesions, age and history of HBV may be risk factors associated with the PA-TACE timing (Figure 3A). In the RFS, multivariate logistic regression analysis found that independent predictors of the PA-TACE timing included gender (OR=2.099,95% CI,1.021-4.312, P<0.05) and history of HBV (OR=2.886, 95%CI,1.723-4.835, P<0.001) (Figure 3B). The values of Nagelkerke's R2 were 0.224, while the results of the Hosmer–Lemeshow test were 0.762 in RFS analysis. These results showed that the overall model fit was good, with a median effect size.

The PA-TACE timing included in cox analysis of prognosis of training cohort

Cox regression analysis was used to explore the effect of the PA-TACE timing on the prognosis of HCC. Univariate Cox analysis showed that TAFP, TBIL, AFP, KI-67, tumor size, MVI and the PA-TACE timing were risk factors for RFS in HCC patients (Figures 3C, D). Then, multivariate Cox analysis showed that Ki-67(HR=1.014, 95%CI,1.007-1.020, P<0.001), tumor size(HR=1.056, 95%CI,1.021-1.092, P=0.001), MVI(HR=1.503, 95%CI,1.114-2.028, P<0.01) and the PA-TACE timing (HR=1.515, 95%CI,1.139-2.015, P<0.01) were independent prognostic factors for RFS in HCC patients.

Development and validation of the nomogram for the prognosis of HCC

To predict the prognosis of HCC patients, a nomogram was developed based on the training cohort that integrated the PA-TACE timing with significant clinical characteristics, such as Ki-67, tumor size and MVI, for RFS (Figure 4A). The ROC curve and AUC

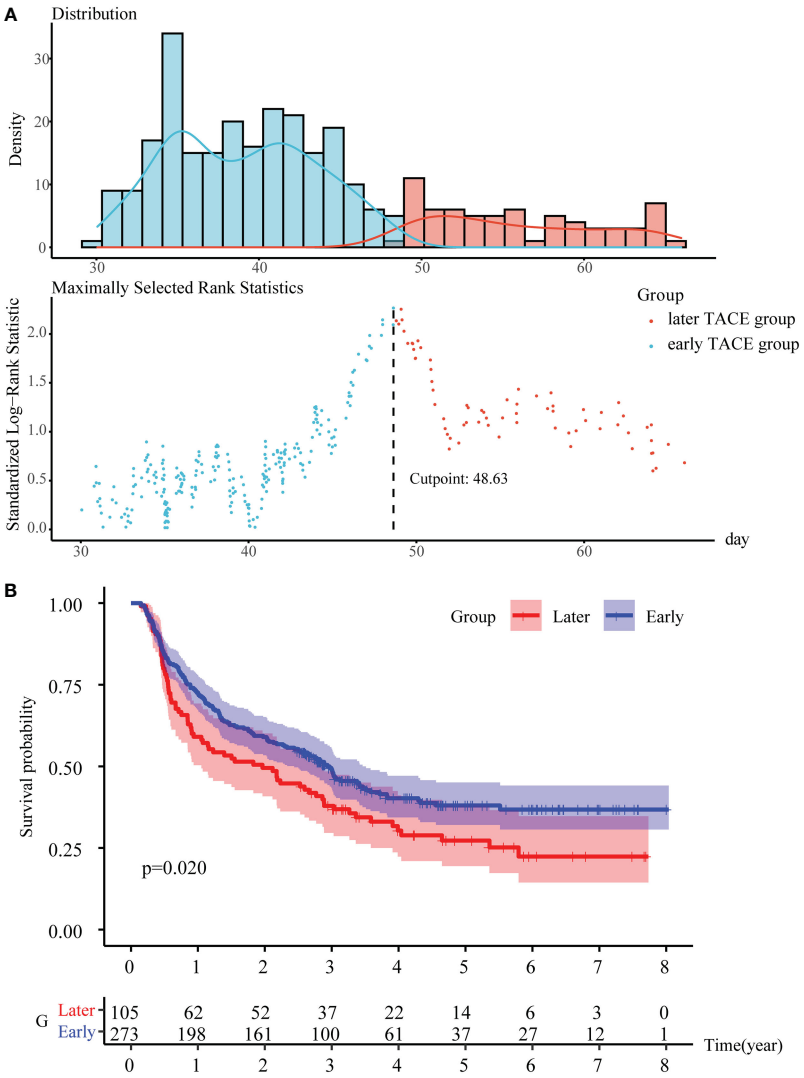

FIGURE 2
To determine the PA-TACE time cutoff values with significant prognostic differences. **(A)** Use the "survminer" package to get the optimal cutoff value for PA-TACE time. **(B)** K-M survival analysis of the early and later TACE groups for RFS. Abbreviations: PA-TACE, postoperative adjuvant TACE; RFS, disease-free survival.

were calculated to evaluate and compare the discriminatory power of the nomogram model. The nomogram showed good predictive performance on the ROC curve. It was observed that the AUC values for 1-, 3- and 5-year RFS were 0.699, 0.685 and 0.700, respectively (Figures 4B–D). When comparing the constructed nomogram with the ideal model, the calibration plot showed good performance (Figure 4E). DCA also confirmed the predictive capacity of the nomogram (Figure 4F).

Internal validation was performed based on gender (male vs. female), age (> 65 years vs. ≤65 years), and BMI (normal vs. abnormal) groupings to further validate the predictive power of the model for RFS. The results showed good predictive performance of the nomogram model for RFS in both the male and female subgroups (Figures 5A, B), the >65 and ≤65 age subgroups (Figures 5C, D), and the normal and abnormal BMI subgroups (Figures 5E, F). In the validation cohort, the 1-year and 2-year C-index of the nomogram were 0.698 and 0.697, respectively (Figures 6A, B). In addition, for the validation cohort, the 1-year and 2-year calibration plot of external validation of nomogram model performed well (Figure 6C). Furthermore, conventional prognostic evaluation systems, such as the Milan criteria (MC) (30), Albumin-Bilirubin (ALBI) grade and Glasgow Prognostic Score (GPS) (31, 32), were compared with the established nomogram to confirm which prognostic model was more reasonable and efficient. Our nomogram outperformed the conventional prognostic evaluation systems for RFS (Figures 6D–F) as measured by ROC curves of 1-, 3- and 5-year.

Safety of TACE treatment and treatment after recurrence

Table 3 summarizes the adverse events (AEs) related to PA-TACE in HCC patients. Overall, we found that most AEs were mild

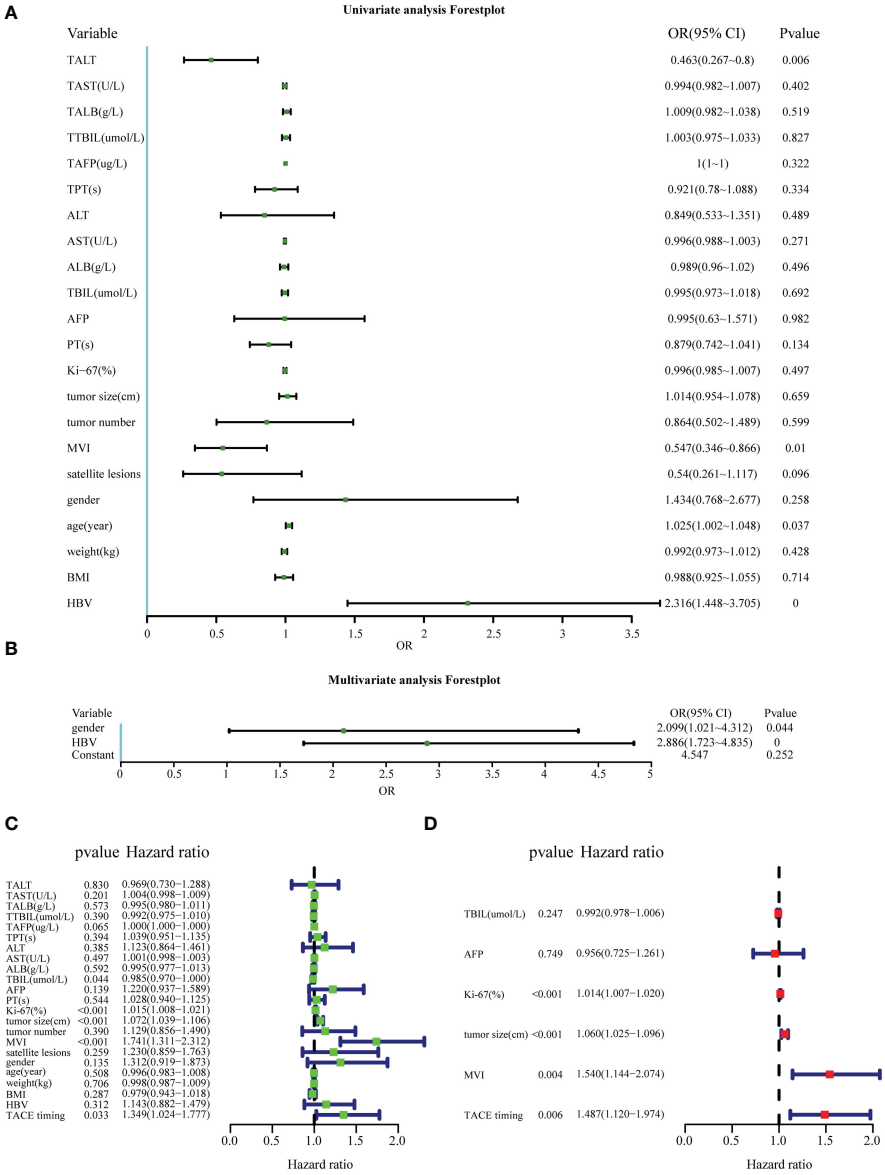

FIGURE 3
Factors affecting the PA-TACE timing and the prognosis of HCC. **(A, B)** Univariate and multivariate logistic analyses to evaluate the factors affecting the PA-TACE timing for RFS. **(C, D)** Univariate and multivariate Cox analyses to evaluate independent prognostic factors of HCC for RFS. ALT, alanine aminotransaminase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; AFP, serum alpha- fetoprotein; PT, prothrombin time; MVI, microvascular invasion; BMI, body mass index. The indicators before PA-TACE were displayed as "T + indicators", such as "TALT".

and manageable, and no toxicity-associated deaths occurred in this study. Nausea/vomiting (33.07%), pain (14.55%) and fever (13.49%) were the most common AEs. A few patients developed liver dysfunction (1.06%), leukopenia (0.53%) or thrombocytopenia (0.53%). No grade 3 or 4 AEs were observed based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

The patients in our study received subsequent antitumor therapies after recurrence, including TACE (40.52%), locoregional ablation (13.36%), hepatectomy (3.02%), targeted therapy and immunotherapy (14.66%) (Table 4). There were 34 patients who received targeted therapy and immunotherapy at the time of recurrence or suspected recurrence. We analyzed the effects of targeted therapy and immunotherapy on patients' OS in Table 5. The analysis results showed that the OS of patients with targeted and immunotherapy was better than that of patients without targeted and immunotherapy, although there was no statistical difference (P>0.05).

Discussion

The 5-year recurrence rate after radical resection of HCC is as high as 60-70% (6, 7), which is an important reason for the poor survival outcomes of HCC patients (6, 33). A variety of adjuvant therapies, including interferon (11), capecitabine (12), hepatic

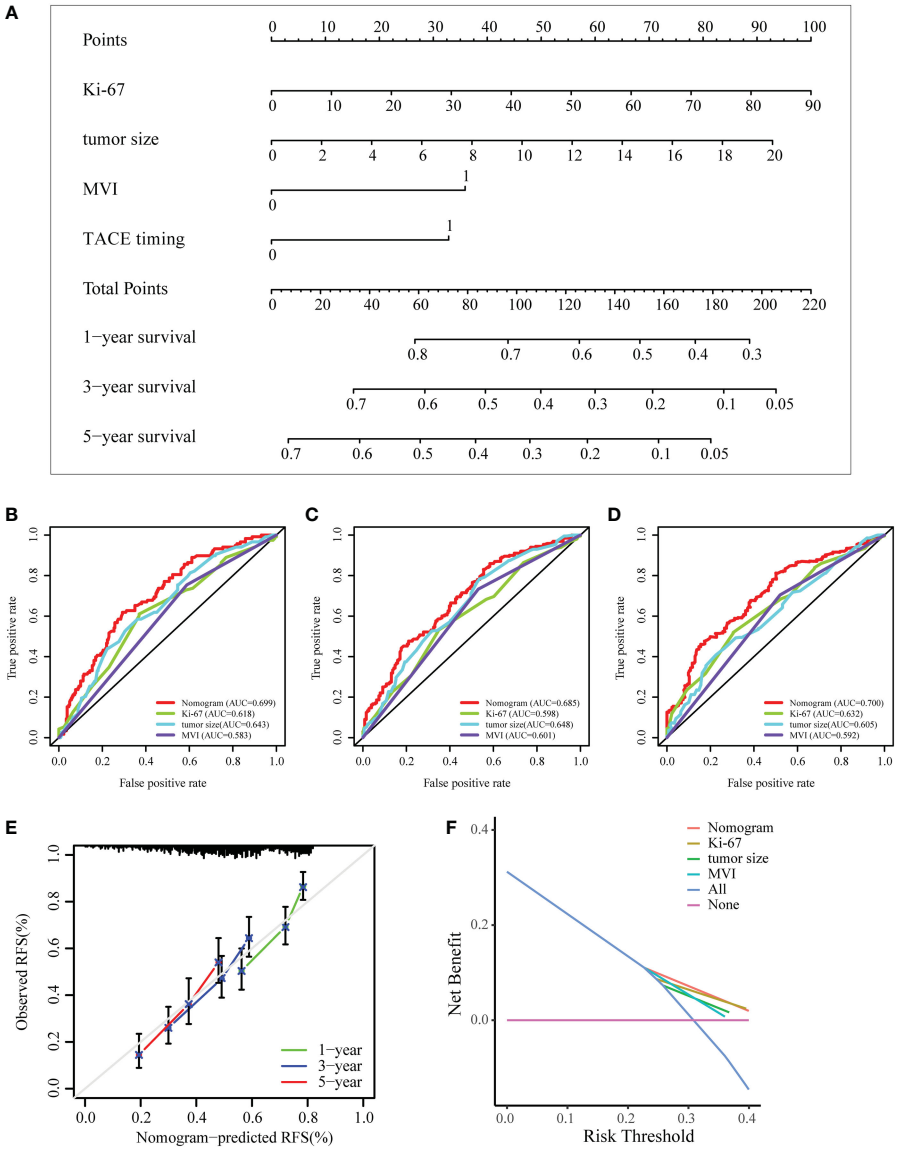

FIGURE 4
Development and validation of a nomogram for the prognosis of HCC. **(A)** Nomogram to evaluate the prognosis of HCC for RFS. **(B–D)** ROC curves of the model predicting the 1-, 3- and 5-year RFS of HCC patients. **(E, F)** The calibration plot and DCA of the nomogram for RFS. ROC, receiver operating characteristic curve; DCA, decision curve analysis; MVI, microvascular invasion.

arterial infusion chemotherapy (13), targeted therapy and immunotherapy (14, 15), have been reported with limited success. In the STORM trial of adjuvant sorafenib for HCC after resection or ablation, the primary endpoint of prolonged RFS was not reached (14). In recent years, a number of retrospective studies and prospective RCT trials have shown that PA-TACE treatment after radical resection of HCC can significantly reduce the tumor recurrence rate and improve the RFS and OS of patients with high-risk recurrence factors (18, 19, 34). As an important adjuvant therapy, TACE has formed a standardization of the technique to a certain extent through long-term development.

Conventional TACE (cTACE), which uses Lipiodol, and TACE with drug-eluting beads (DEB-TACE) are the two types of TACE techniques (35–38). The two TACE technologies are similar in tumor response and survival, while DEB-TACE has less systemic toxicity and adverse events (AEs) (37, 39). The chemotherapeutic agents used in TACE are generally doxorubicin or cisplatin (40, 41), and the choice of chemotherapeutic agent for TACE may not significantly affect the prognosis of patients (42). The fixed TACE schedule and tumor response guided retreatment (treatment on demand) strategy are both considered in retreatment decision-making, but fixed treatment strategies may have deleterious effects on liver function (43). The frequency of TACE also varies widely and is spaced as close as 2 weeks or as far as 8 weeks apart (41, 44). The STATE score, HAP score and ABCR score were developed to evaluate the criteria for the first and repeated TACE treatment of patients with intermediate stage HCC (BCLC) (45–47). These tools have shown limited predictive value. However, the PA-TACE timing after radical resection in patients with high-risk recurrence factors has not been reported. The PA-TACE time mentioned in

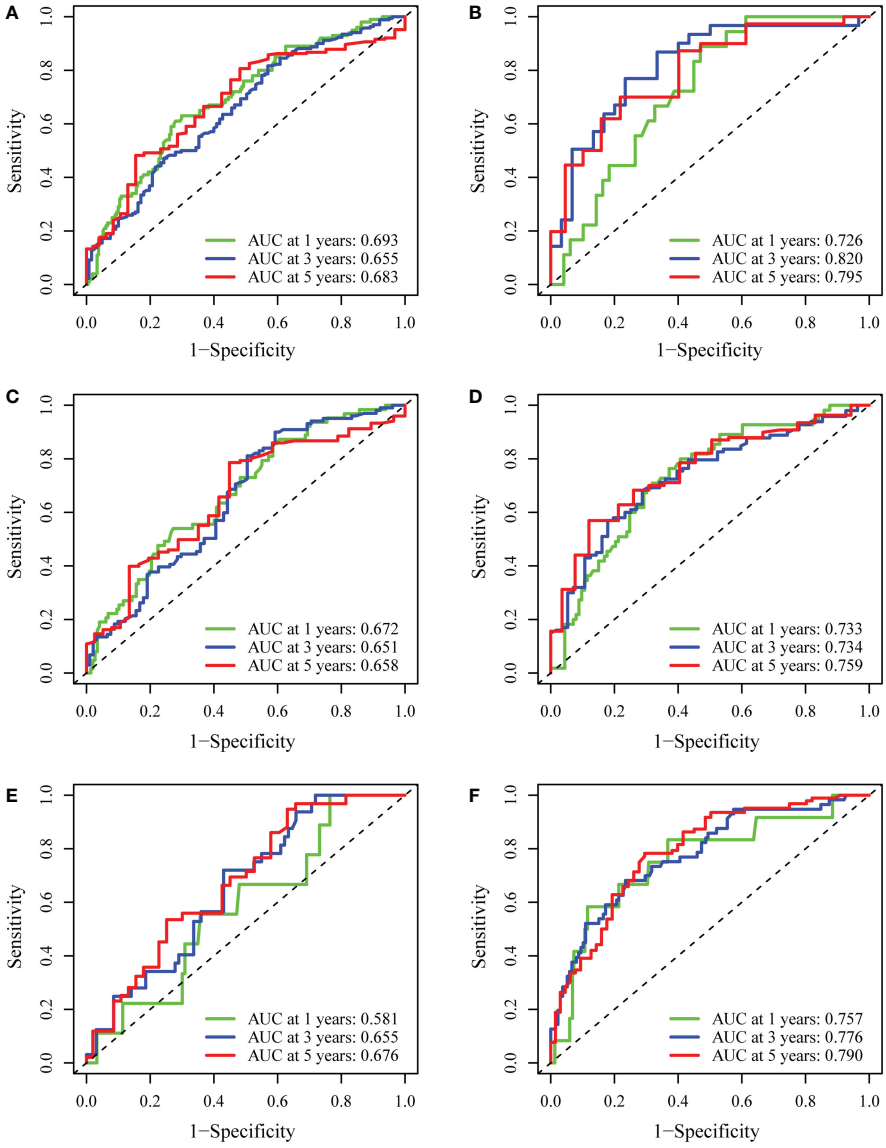

FIGURE 5
Internal validation of the nomogram model. **(A, B)** The predictive performance of the nomogram based on gender (male vs. female) for RFS. **(C, D)** The predictive performance of the nomogram based on age (>65 vs. ≤65) for RFS. **(E, F)** The predictive performance of the nomogram based on BMI (normal vs. abnormal) for RFS.

various studies is approximately one month based on experience (17–19, 34). This study demonstrated that the PA-TACE timing after radical resection was an independent prognostic factor for HCC patients with high-risk recurrence factors.

In this retrospective study, the usual time for patients to undergo PA-TACE was approximately one month. Patients who undergo PA-TACE prematurely are prone to liver failure and other serious complications, as their liver function has not fully recovered, their albumin level is low, and infection has not been completely controlled (48–51). Furthermore, when major abdominal surgery is performed, such as hepatectomy, growth factors and proinflammatory cytokines (such as macrophage inflammatory protein-2, interleukin-6, and tumor necrosis factor alpha) are released that promote regeneration of the remaining liver tissue but may also inadvertently enhance the proliferation of these remaining tumor cells (52–54). Therefore, it is important to administer PA-TACE treatment before the tumor becomes difficult to control. Nevertheless, whether patients follow doctors' recommendations is largely determined by their socioeconomic status and compliance with doctors. Interestingly, the phenomena found in our study can partially explain the above theory. ALT (TACE) in the early TACE group was higher than that in the later TACE group (31.2, 20.93-48 vs. 25, 19.08-36.18, P<0.01), while the age of the later TACE group was older than that of the early TACE group (60, 52.25-68 vs. 64, 56.75-69, P<0.05) in training cohort. One possible reason is that the elderly are less motivated with regard to disease treatment than relatively young people. The difference in the PA-TACE timing is thought to explain the different prognoses of HCC patients.

Using the optimal cutoff value method, we determined that the grouping cutoff values for RFS in the samples were 48.63 days, and

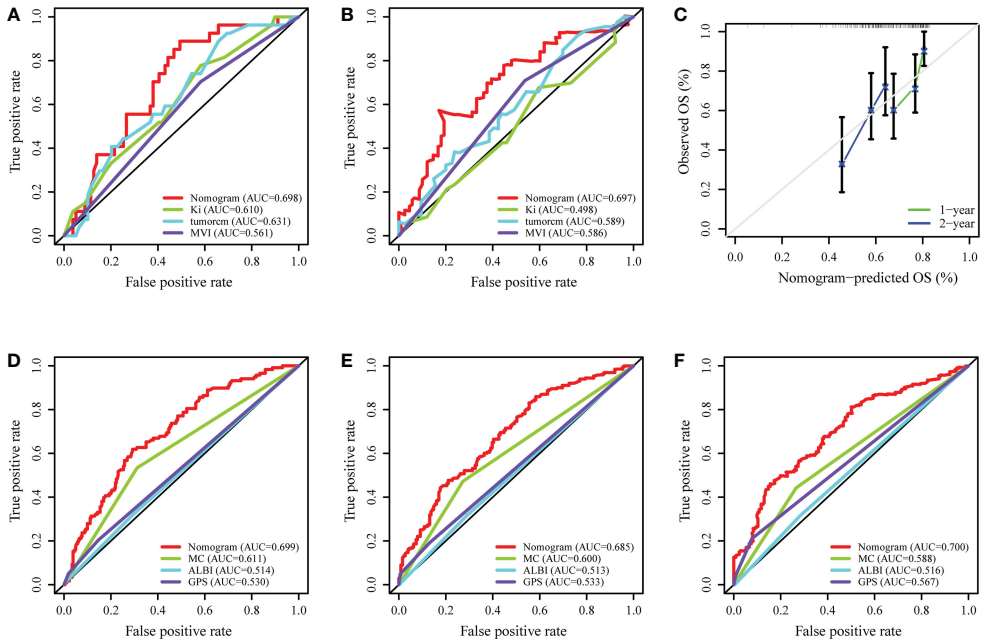

FIGURE 6
External validation and comparison of the nomogram model with the conventional prognostic evaluation systems. **(A, B)** ROC curves of the nomogram model predicting the 1- and 2-year RFS in validation cohort. **(C)** The calibration plot of the nomogram for RFS in validation cohort. **(D–F)** ROC curves of the nomogram model and the conventional prognostic evaluation systems predicting the 1-, 3- and 5-year RFS of HCC patients. MC, Milan criteria; ALBI, Albumin-Bilirubin grade; GPS, Glasgow Prognostic Score.

TABLE 3 The adverse events (AEs) related to PA-TACE in HCC patients.

Adverse events	Total Patients (n=378)	Early TACE group (n=272)		Later TACE group (n=106)	
Grade	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
Nausea/vomiting	125 (33.07)	0	87 (31.99)	0	38 (35.85)	0
Pain	55 (14.55)	0	39 (14.34)	0	16 (15.09)	0
Fever	51 (13.49)	0	37 (13.60)	0	14 (13.21)	0
Leukopenia	2 (0.53)	0	0	0	2 (1.89)	0
Thrombocytopenia	2 (0.53)	0	0	0	2 (1.89)	0
Liver dysfunction	4 (1.06)	0	3 (1.10)	0	1 (0.94)	0

the prognosis difference between the two groups was statistically significant. Logistic regression analysis showed that gender and history of HBV may be significant indicators to distinguish patients in early and later TACE groups. These indicators can provide guidance for the PA-TACE timing. We recommend that HCC patients with high-risk recurrence factors should undergo PA-TACE approximately one month after surgery and no later than 48.63 days. A large number of studies have confirmed that men have

TABLE 4 The subsequent antitumor therapies after recurrence.

	Total Patients (n=378)	Early TACE group (n=272)	Later TACE group (n=106)
recurrence	232 (61.38)	157 (57.72)	75 (70.75)
TACE	94 (40.52)	67 (42.68)	27 (36)
Locoregional ablation	31 (13.36)	21 (13.38)	10 (13.33)
Hepatectomy	7 (3.02)	5 (3.18)	2 (2.67)
Targeted therapy and immunotherapy	34 (14.66)	21 (13.38)	13 (17.33)
Conservative treatment	66 (28.45)	43 (27.39)	23 (30.67)

TABLE 5 Effects of targeted therapy and immunotherapy on OS in HCC patients after recurrence.

	Targeted therapy and immunotherapy (n=34)	No-targeted therapy and immunotherapy (n=344)	P value
Total	4.45 (2.83-5.53)	3.36 (2.60-4.92)	0.073
Early TACE group	4.36 (2.82-5.51)	3.38 (2.65-4.93)	0.179
Later TACE group	4.62 (2.75-5.62)	3.24 (2.22-4.90)	0.227

a greater risk of developing HCC than women worldwide, 2.35-fold more men were expected to die from HCC than women, and the same is true in China (55). However, it is not clear why men are more likely to develop HCC than women. The possible reasons are that the lower adiponectin levels found in men account for the increased incidence of HCC in men (56), and the different roles of the sex hormones (including androgens and estrogens and their corresponding receptors) and inflammatory mediators (IL-6, etc.) in the progression of HCC in men and women (57, 58). Due to the high incidence and mortality of HCC in male patients, we recommend that PA-TACE should particularly be performed in time after radical resection in male patients.

HBV was the first virus associated with the development of HCC and is the leading cause of HCC worldwide (59, 60). As a major aetiological factor, HBV infection changes the hepatic microenvironment, induces an inflammatory response, promotes angiogenesis and vascular invasion and affects the prognosis of HCC patients (61, 62). Similarly, we suggest that HCC patients with high-risk recurrence factors and HBV infection after radical resection should receive PA-TACE treatment in time under the guidance of doctors to obtain the best treatment outcome. Univariate and multivariate Cox regression analyses finally proved that the PA-TACE timing, Ki-67, tumor size and MVI were independent prognostic factors for HCC patients with high-risk recurrence factors. Ki-67 is a marker of proliferation. High-level Ki-67 expression in HCC tumors is associated with more rapid early recurrence (63, 64). Tumor size plays an important role in predicting HCC progression, and the risk of recurrence increases significantly as the tumor grows (65, 66). MVI is now widely used as a tool for assessing tumor aggressiveness and has been proven to be correlated with tumor recurrence and prognosis (67, 68). The nomogram model is more accurate in predicting RFS at 1, 3, and 5 years than individual clinicopathological risk factors. Additionally, the calibration curve and DCA results of the retest of the nomogram also showed a high level of prediction accuracy and good net benefit for RFS. Subgroup analysis suggested that the nomogram model provided predictive benefit to all the subpopulations. In external validation, the 1-year, 2-year calibration plot and ROC curves of nomogram model performed well. Furthermore, compared with conventional prognostic evaluation systems such as the Milan criteria (MC), albumin-bilirubin (ALBI) grade and Glasgow Prognostic Score (GPS), our nomogram still revealed good superiority.

Targeted therapy and immunotherapy after radical resection of HCC can improve the prognosis of patients (69, 70). There were 34 patients who received targeted therapy and immunotherapy at the time of recurrence or suspected recurrence. The results showed that targeted therapy and immunotherapy can improve the OS of HCC patients with recurrence, but further research was still needed.

There are several limitations to the present study. First, this was a retrospective, single-center study. A prospective, well-designed, multicenter, and randomized trial is required to validate the significance of the PA-TACE timing in HCC prognosis. Second, the majority of patients in this study (52.69%) had HBV-associated HCC. These results may not generalize to other causes of HCC. Third, all of the samples originated from China. Consequently, our findings may not be generalizable beyond Eastern Asia.

In conclusion, the PA-TACE timing is an independent factor affecting the prognosis of HCC patients with high-risk recurrence factors after radical resection. We have proposed that the recommended time for PA-TACE is about one month, no later than 48.63 days. Then, the gender and history of HBV are guiding indicators for PA-TACE. Moreover, based on multivariate Cox regression analysis, we established a nomogram model to predict the prognosis of HCC patients by combining the PA-TACE timing, Ki-67, tumor size and MVI. This study can provide personalized assistance for HCC patients with high-risk recurrence factors to undergo PA-TACE treatment and improve the survival outcomes of patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The Affiliated Hospital of Qingdao University Research Ethics Committee approved the study protocol. The patients/participants provided their written informed consent to participate in this study.

Author contributions

HS: Manuscript writing, research design, data collection, management and data analysis. HW: Research design, manuscript

writing, data collection and data analysis. YW: Data collection, management and data analysis. WZ: Data collection and analysis. YM: Data collection and analysis. ZL: Data collection and analysis. WG: Project development and manuscript editing. BH: Project development, research design, and manuscript editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Dexmedetomidine ameliorates liver injury and maintains liver function in patients with hepatocellular carcinoma after hepatectomy: a retrospective cohort study with propensity score matching

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Background: Although dexmedetomidine (DEX) is widely used during the perioperative period in patients with hepatocellular carcinoma (HCC), its clinical effects on liver function and postoperative inflammation are unclear. This study aimed to explore effects of DEX on postoperative liver function and inflammation in patients with HCC after hepatectomy.

Methods: A retrospective cohort study with propensity score matching was performed. A total of 494 patients who underwent hepatectomy from June 2019 to July 2020 and fulfilled the eligibility criteria were included in this study. Baseline data, liver function indexes and inflammation-related biomarkers were collected and compared between the two groups. Survival analysis was conducted to investigate the effects of DEX on the overall survival (OS) of patients. Propensity score matching (PSM) was used to minimize bias between the two groups.

Results: The study cohort comprised 189 patients in the DEX-free group and 305 patients in the DEX group. Patients in the DEX group had lower levels of alanine transaminase (ALT, $P = 0.018$) and lactate dehydrogenase (LDH, $P = 0.046$) and higher level of serum albumin (ALB, $P < 0.001$) than patients in the DEX-free group before discharge. A total of 107 pairs of patients were successfully matched by PSM. Results consistently suggested that ALT and LDH levels were significantly lower ($P = 0.044$ and $P = 0.046$, respectively) and ALB levels were significantly higher ($P = 0.002$) in the DEX group than in the DEX-free group in the early postoperative period. No significant differences of inflammation-related biomarkers were observed between two groups after PSM. Neither the Kaplan–

Meier survival analysis nor the multiple Cox regression survival analysis identified DEX as a contributing factor that would affect the OS of patients after PSM.

Conclusion: DEX exerts protective effects on liver function while has little effects on inflammation-related biomarkers in the early postoperative period in patients undergoing hepatectomy due to HCC.

KEYWORDS

hepatocellular carcinoma, liver injury, inflammation, perioperative organ damage, dexmedetomidine

1 Introduction

Hepatocellular carcinoma (HCC) has one of the highest incidence rates among cancers worldwide and has become the third leading cause of death among all types of cancers (1, 2). Especially, in China, HCC is ranked as the second major cause of cancer-related death owing to the prevalence of hepatitis virus (3). It causes heavy burden on global health.

Despite the implementation of multiple treatment approaches such as ablation, liver transplantation, immune checkpoints inhibitors and CAR-T (chimeric antigen receptor T) immunotherapy for HCC in the clinic, hepatectomy remains the preferred option for patients with resectable HCC (4). Although hepatectomy effectively excises the primary tumor, it simultaneously causes unavoidable liver injury. Meanwhile, ischemia–reperfusion injury (IRI) induced by inflow occlusion during hepatectomy significantly activates local and systemic inflammatory responses, oxidative stress injury, and multiple organ injury, including the liver, kidney, and heart (4–6), which would even result in dangerous postoperative complications such as hepatic failure, renal dysfunction, and irreversible myocardial injury (4). Therefore, identifying the method to minimize liver injury and ameliorate liver function during hepatectomy will be highly clinically significant for patients with HCC.

As a highly selective α_2-receptor agonist, dexmedetomidine (DEX) is widely used in clinical anesthesia for satisfactory sedation and analgesia without causing respiratory depression and hemodynamic instability (7). Moreover, animal and human studies have reported that DEX is effective in preventing postoperative delirium, promoting liver regeneration, inhibiting sepsis-induced systemic inflammatory response and injury, and improving the functions of important organs such as the kidney, lung, intestinal tract, and heart postoperatively or in the intensive care unit (ICU) (8–11). Several fundamental experiments have proved the protective effects of DEX on liver function after surgery by demonstrating that perioperative DEX use significantly reduced inflammatory response and oxidative stress injury in hepatectomy or liver transplantation surgeries (12–14).

Nevertheless, the effects of DEX on liver function were primarily investigated in animal studies, and only a few clinical studies with small sample sizes have investigated this issue in patients undergoing hepatectomy (6, 15, 16). Therefore, we conducted this retrospective cohort study with a suitable sample size and using propensity score matching (PSM) to determine the effects of DEX on liver function in patients undergoing surgery due to HCC.

2 Methods

2.1 Study design

This retrospective, single-center cohort study was conducted in the Eastern Hepatobiliary Surgery Hospital, Shanghai, China. This study was approved by the Eastern Hepatobiliary Surgery Hospital's Institutional Review Board (Number: EHBHKY2021-K-011). We included only those patients who granted authorization for future research use of their medical records. This study was conducted according to the Declaration of Helsinki and was consistent with the STROBE criteria.

2.2 Participants

Patients aged >18 years, with American Society of Anesthesiologists (ASA) scores of I–III and Child–Pugh stages A and B, and who underwent elective hepatectomy for HCC treatment from June 2019 to July 2020 were included in this study. The exclusion criteria were as follows: (1) malignant tumors in other organs, (2) a combination of thermal ablation or chemoablation during hepatectomy, (3) any congenital liver disease (e.g., polycystic liver disease and Wilson's disease) or autoimmune liver disease, (4) liver failure before surgery [defined according to guidelines (17)], and (5) other severe organ failure before surgery (i.e., heart failure was defined as a left ventricular ejection fraction of < 35%, and renal failure was defined as a serum creatinine level of >442 μmol/L) (18, 19).

2.3 Intervention, anesthesia, and surgical anesthesia care

Patients were divided into the DEX or DEX-free group based on whether they received intravenous DEX or not during the

perioperative period. As DEX is not available in the ICU or wards in the Eastern Hepatobiliary Surgery Hospital, patients in the DEX group were infused with DEX only during the surgery. The dosage of DEX was collected from the digital medical records system.

Patients in both groups underwent hepatectomy under general anesthesia. They were monitored according to the ASA monitoring standards. Based on the preference of anesthetists, patients received propofol, midazolam (optional), fentanyl/sufentanil/oxycodone, and rocuronium for anesthesia induction. General anesthesia was maintained with sevoflurane, rocuronium, sufentanil/remifentanil, propofol (optional), and DEX (optional). Mechanical ventilation was initiated after tracheal intubation, and $P_{ET}CO_2$ was maintained in the range of 35–45 mmHg. The mean arterial blood pressure was maintained at >60 mmHg with an infusion of Ringer's lactate solution and artificial colloid, or vasoactive agents when needed, during the operation. Blood transfusion was initiated when the patient's hemoglobin level decreased to <7 mg/dl or decided by the anesthesiologists based on the patients' age, hemodynamic stability, and presurgical hemoglobin levels when the hemoglobin level was 7–10 mg/dl.

For patients who received DEX during surgery, DEX was diluted in 0.9% saline to a final concentration of 4 μg/ml, and a total dose of 0.5–1.0 μg/kg was injected through an intravenous pump during anesthesia induction and maintenance, as determined by the anesthesiologist's preference.

Standard hepatectomy was performed with or without temporary hepatic inflow occlusion by experienced liver surgeons. The duration of hepatic inflow occlusion was determined by surgeons. The same therapy guidelines were followed by all surgical teams.

Patients were transferred to the ICU or recovered in the post-anesthesia care unit after surgery, as decided by surgeons. Postoperative analgesia was provided by patient-controlled intravenous analgesia (PCIA) based on a consensus between the patient and the clinical team. For PCIA, an intravenous pump with 2.0 μg/kg sufentanil and 100 mg flurbiprofen axetil in 100 ml normal saline was used. The infusion rate was 2 ml/h with 15-min block time. In general, the pump was maintained for the first 2 days after the operation.

2.4 Variables and data sources

Preoperative clinical characteristics of the patients, including gender, age, height, weight, ASA score, Child–Pugh stage, TNM stage, and comorbidity, were recorded. Intraoperative and postoperative factors, including tumor location, tumor size, tumor number, surgery information, types and doses of intraoperative anesthetics, blood transfusion, fluid balance, postoperative analgesia, ICU stay, and postoperative complications, were also collected. Tumor size was defined as the maximum diameter of the tumor or the average of the maximum diameter when there are more than one tumor. The expression levels of liver function biomarkers, including serum alanine transaminase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), total bilirubin (TBIL), and serum albumin (ALB), were collected at three time points: before operation, 24 h after operation, and before discharge (the latest biochemical detection before discharge from the hospital). The levels of inflammation biomarkers, including serum C-reactive protein (CRP), WBC, and percentage of neutrophils (N%) in peripheral blood, were also collected at the abovementioned three time points.

All data were retrieved from the digital medical system or paper medical records. Two trained researchers completed the data collection and entered the data into the Excel or EpiData system. Data regarding the survival condition of patients were obtained from the digital medical system, surgeons, or telephone follow-up. Data were censored for patients who were alive at the follow-up closure date (April 7, 2022).

2.5 Study outcomes

The primary outcome was the serum ALT level. The secondary outcomes included the expression levels of inflammatory biomarkers (serum CRP, WBC number, and N%); the serum levels of AST, TBIL, LDH, and ALB; and the overall survival (OS) of the patients.

2.6 Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics 23.0 (SPSS Inc., Armonk, NY, USA). Categorical variables were expressed as number (n), and continuous variables were expressed as mean ± standard deviation or mean ± standard error (SEM) or median [25% interquartile range, 75% interquartile range] based on normality. Student's *t*-test or the Mann–Whitney U test was conducted to compare continuous variables. Categorical variables were compared using the $\chi 2$ test or Fisher's exact test, where appropriate. The differences in the levels of serum biomarkers reflecting liver function and inflammation were analyzed using two-way repeated analysis with the Bonferroni correction. All statistical tests were two-sided, and a P value of <0.05 was considered statistically significant.

The Kaplan–Meier survival analysis was performed, and curves were generated using the log-rank test to identify the differences in OS between the two groups. The curve for cumulative risk was also generated. Next, a multivariable Cox regression analysis was conducted to adjust potential bias. Potential risk factors with $P <$ 0.05 in the univariable Cox analyses were included in the multivariable Cox regression analysis.

The PSM method was applied to eliminate potential bias between the two groups. A logistic regression model of PSM was constructed using the covariates of ASA score, TNM stage, viral hepatitis, cirrhosis, TACE before surgery, tumor size, duration of hepatic inflow occlusion, volume of bleeding, plasma transfusion, RBC transfusion, volume of crystalloid fluid, volume of colloidal fluid, dosage of midazolam, and dosage of NSAIDs. We applied 1:1 nearest neighbor matching without replacement to ensure that conditional bias was minimized. The caliper width was 0.1.

3 Results

As depicted in Figure 1, a total of 1069 patients who underwent hepatectomy from June 1, 2019, to July 31, 2020, were screened for the study. Then, 494 who fulfilled the criteria were finally enrolled and divided into the DEX group (n = 305) and DEX-free group (n = 189). In addition to DEX dosage, several other baseline characteristics of the patients, including the ASA score, hepatic inflow occlusion duration, volume of bleeding, and midazolam dosage, were significantly different between the two groups, as shown in Table 1. To eliminate bias between the two groups, PSM was performed, and 107 pairs of patients were successfully matched finally. No significant differences were observed in the PSM score and baseline characteristics, except the dosage of DEX, between the two groups after PSM (Table 2).

3.1 Primary endpoint

Two-way repeated analysis of serum ALT levels revealed no difference in ALT levels between the two groups before surgery (Figure 2A). Although the ALT levels in both groups were generally higher postoperatively than preoperative baseline levels, the levels were significantly lower in the DEX group than in the DEX-free group after surgery (P = 0.018 before PSM and P = 0.044 after PSM, Figure 2A). *Post hoc* analysis further showed that the difference between the two groups was significant before discharge (P = 0.003 before PSM and P = 0.005 after PSM), but not at 24 h after surgery, although the difference appeared to be greater at this time point (Figure 2A).

3.2 Effects of DEX on other liver function biomarkers

The serum levels of AST, LDH, TBIL, and ALB showed no differences between the two groups before surgery (Figures 2, 3). As shown in Figure 2B, the LDH serum levels were significantly lower in the DEX group than in the DEX-free group postoperatively (P = 0.046 before PSM and P = 0.046 after PSM). Interestingly, the serum levels of AST and TBIL remained comparable between the two groups at all the examined time points both before and after PSM (Figures 3A, B).

The results also revealed that the ALB serum levels were higher in the DEX group than in the DEX-free group after surgery (Figure 2C). The difference was more obvious at 24 h after surgery (P < 0.001 for both before and after PSM) and remained significant till before discharge (P = 0.008 before PSM and P = 0.054 after PSM). This finding indicated that DEX might not only alleviate liver injury but also maintain the productive function of the liver.

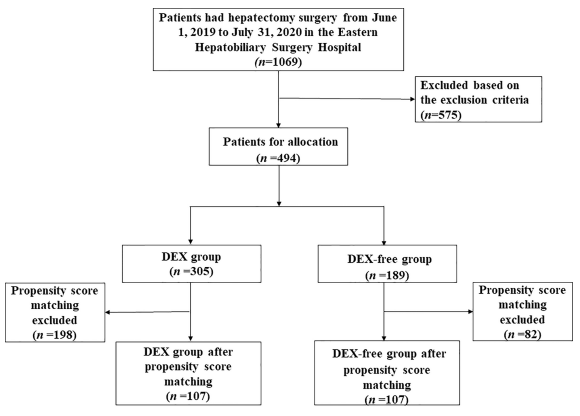

FIGURE 1
Flow diagram detailing the selection process for patients in this study.

3.3 Effects of DEX on inflammation-related biomarkers

Although there were no differences in serum CRP levels and peripheral WBC count between the two groups at all time points (Figures 3C, D), the N% in peripheral blood was slightly but significantly higher in the DEX group at 24 h after surgery than in the DEX-free group before PSM (P = 0.001, Figure 3E). However, the difference was absent between the two groups after PSM (P = 0.496, Figure 3E). These results suggested that DEX did not have much influence on postoperative inflammation in patients undergoing hepatectomy.

3.4 Effects of DEX on the OS of patients

Before PSM, both univariable and multivariable Cox regression analyses of OS suggested a worse OS for patients in the DEX group (Supplementary Table 1, Supplementary Figure 1). However, there was no difference in the OS of patients between the two groups (P = 0.059, HR = 1.96, 95% CI: 0.96–3.98) as evaluated by the Kaplan–Meier survival analysis after PSM (Figure 4). We next included all the risk factors which P < 0.05 in univariable Cox analyses into a multivariable Cox regression analysis to adjust potential bias. As shown in Table 3, there was still no difference in the OS between the two groups (P = 0.076, HR = 2.00, 95% CI: 0.93–4.29). Interestingly, the multiple Cox regression analysis suggested that drinking, PVTT, and tumor size were independent risk factors for the OS of patients undergoing hepatectomy due to HCC.

4 Discussion

This retrospective cohort study suggests possible protective effects of DEX on liver function in patients with HCC who underwent hepatectomy. Perioperative DEX use may not only reduce liver injury but also improve the liver function of producing ALB during hepatectomy. Little effects of DEX on early postoperative inflammation were found between two groups.

TABLE 1 Clinical characteristics of patients between two groups before PSM.

	DEX-free group (n=189)	DEX group (n=305)	*P* value
Preoperative			
Gender (male/female)	153/36	246/59	0.94
Age (year)	57.1 (10.6)	56.1 (11.2)	0.32
Height (cm)	167.1 (6.9)	168.0 (6.1)	0.15
Weight (kg)	67.6 (11.5)	67.3 (9.0)	0.77
ASA stage*			
I and II	182 (97.3%)	241 (79.8%)	**0.00**
III	5 (2.7%)	61 (20.2%)	
Child-Pugh stage (A/B)	189/0	304/1	1.00
TNM stage*			
I	103 (54.5%)	169 (56.5%)	0.53
II	77 (40.7%)	110 (36.8%)	
III and IV	9 (4.8%)	20 (6.7%)	
Hypertension (Yes/No)	40/149	75/230	0.38
Diabetes (Yes/No)	21/168	37/268	0.73
Smoking (Yes/No)	71/118	139/166	0.08
Alcohol drinking (Yes/No)	56/133	91/214	0.96
Viral hepatitis*§ (Yes/No)	145/44	238/54	0.20
HBV-DNA ≥ 50IU/ml* (Yes/No)	74/111	132/171	0.44
Cirrhosis* (Yes/No)	102/86	158/147	0.60
PVTT* (Yes/No)	7/167	18/225	0.15
TACE before surgery (Yes/No)	32/157	40/265	0.24
Intraoperative			
Open/laparoscopic	182/7	290/14	0.63
Left/right/caudate/left + right lobe resection	49/121/2/17	60/206/6/32	0.37
Tumor number (Single/Multiple)	163/26	258/46	0.67
Tumor size (cm)	5.3 (3.7)	5.8 (4.0)	0.18
Length of hepatic inflow occlusion (min)	16 [9, 22]	20 [6, 33]	**0.00**
Volume of bleeding (ml)	200 [200, 400]	300 [200, 500]	**0.00**
Plasma transfusion (Yes/No)	17/172	67/238	**0.00**
RBC transfusion (Yes/No)	17/172	63/242	**0.00**
Crystalloid fluid** (ml)	1500 [1000, 1500]	1000 [1000, 1500]	**0.00**
Colloid fluid** (ml)	500 [500, 500]	700 [500, 1000]	**0.00**
ALB transfusion (g)	20 [20, 20]	20 [20, 20]	0.71
Dosage of opioids (equivalent dose of morphine, mg)	159.4 (91.3)	171.3 (97.2)	0.17
NSAIDs§§ (mg)	0 [0, 37.5]	0 [0, 0]	0.18
Midazolam (mg)	2.0 [2.0, 2.0]	2.0 [0.0, 3.0]	**0.00**
DEX (μg)	0	40 [40, 50]	**0.00**

(Continued)

TABLE 1 Continued

	DEX-free group (n=189)	DEX group (n=305)	*P* value
Postoperative			
ICU care (Yes/No)	46/142	88/214	0.26
PCIA (Yes/No)	125/64	212/93	0.43
Postoperative complications			
Fever[§§§] (> 38°C over 48 h)	1 (0.5%)	3 (1.0%)	0.54
Pain	14 (7.4%)	18 (5.9%)	
Bleeding	2 (1.1%)	2 (0.7%)	
Severe PONV[§§§]	1 (0.5%)	0 (0.0%)	

Variables are shown as "mean (SD)", "number (%)" or "median [25% quartile, 75% quartile]". HCC, Hepatocellular carcinoma; DEX, dexmedetomidine; ASA, American Society of Anesthesiologists; TNM, Clinicopathological stage; HBV, hepatitis B viral; PVTT, portal vein tumor thrombus; TACE, transcatheter arterial chemoembolization; RBC, red blood cell; ALB, Albumin; NSAIDs, non-steroidal anti-inflammatory drugs; PONV, postoperative nausea and vomiting; ICU, intensive care unit; PCIA, patient-controlled intravenous analgesia; SD, standard deviation. PSM, propensity score matching.
Bold values mean $P < 0.05$
*Factors with single asterisk indicates patients with missing data.
[§]Viral hepatitis includes HBV and HCV infection.
**Crystalloid fluid means lactated Ringer's solution and colloid fluid means hydroxyethyl starch solution (Voluven) in the studied center.
[§§]NSAIDs means flurbiprofen axetil in the studied center.
[§§§] The body temperature is reflected by the armpit temperature. Severe PONV is defined as episodes of expulsion of gastric contents that need antiemetic treatment.

TABLE 2 Clinical characteristics of HCC patients between two groups after PSM.

	DEX-free group (n=107)	DEX group (n=107)	*P* value
Propensity score	0.49 (0.23)	0.44 (0.23)	0.11
Preoperative			
Gender (male/female)	92/15	87/20	0.36
Age (year)	55.9 (10.6)	54.8 (11.1)	0.49
Height (cm)	167.9 (6.8)	168.0 (5.5)	0.96
Weight (kg)	68.1 (11.4)	67.7 (9.0)	0.77
ASA stage			
I and II	102 (95.3%)	94 (87.9%)	0.09
III	5 (4.7%)	13 (12.1%)	
Child-Pugh stage (A/B)	107/0	107/0	1.00
TNM stage			
I	60 (56.1%)	57 (53.3%)	0.89
II	43 (40.2%)	45 (42.1%)	
III and IV	4 (3.7%)	5 (4.7%)	
Hypertension (Yes/No)	19/88	22/85	0.60
Diabetes (Yes/No)	13/94	15/92	0.69
Smoking (Yes/No)	41/66	42/65	0.89
Alcohol drinking (Yes/No)	31/76	32/75	0.88
Viral hepatitis[§] (Yes/No)	87/20	85/22	0.73
HBV-DNA ≥ 50IU/ml* (Yes/No)	46/61	45/62	0.89
Cirrhosis (Yes/No)	55/52	54/53	0.89

(Continued)

TABLE 2 Continued

	DEX-free group (n=107)	DEX group (n=107)	*P* value
PVTT (Yes/No/Missing)	4/96/7	6/83/18	0.40
TACE before surgery (Yes/No)	20/87	17/90	0.59
Intraoperative			
Open/laparoscopic	105/2	99/8	0.10
Left/right/caudate/left + right lobe resection	28/70/1/8	24/74/2/7	0.85
Tumor number (Single/Multiple)	94/13	91/16	0.55
Tumor size (cm)	5.4 (4.0)	5.5 (3.7)	0.95
Length of hepatic inflow occlusion (min)	17 [9, 23]	15 [0, 29]	0.97
Volume of bleeding (ml)	200 [200, 400]	300 [200, 400]	0.41
Plasma transfusion (Yes/No)	13/94	18/89	0.33
RBC transfusion (Yes/No)	13/94	18/89	0.33
Crystalloid fluid* (ml)	1500 [1000, 1500]	1000 [1000, 1500]	0.56
Colloid fluid* (ml)	500 [500, 500]	500 [500, 750]	0.40
ALB transfusion (g)	20 [20, 20]	20 [20, 20]	0.18
Dosage of opioids (equivalent dose of morphine, mg)	157.8 (90.5)	142.8 (90.8)	0.23
NSAIDs[§§] (mg)	0 [0, 0]	0 [0, 0]	0.43
Midazolam (mg)	2.0 [2.0, 2.0]	2.0 [2.0, 3.0]	0.45
DEX (μg)	0	40 [40, 40]	0.00
Postoperative			
ICU care (Yes/No)	30/76	34/70	0.49
PCIA (Yes/No)	68/39	67/40	0.89
Postoperative complications			
Fever[§§§] (> 38°C over 48 h)	0 (0.0%)	1 (0.9%)	0.70
Pain	8 (7.5%)	8 (7.5%)	
Bleeding	2 (1.9%)	1 (0.9%)	
Severe PONV[§§§]	0 (0.0%)	0 (0.0%)	

Variables are shown as "mean (SD)", "number (%)" or "median [25% quartile, 75% quartile]". HCC, Hepatocellular carcinoma; DEX, dexmedetomidine; ASA, American Society of Anesthesiologists; TNM, Clinicopathological stage; HBV, hepatitis B viral; PVTT, portal vein tumor thrombus; TACE, transcatheter arterial chemoembolization; RBC, red blood cell; ALB, Albumin; NSAIDs, non-steroidal anti-inflammatory drugs; PONV, postoperative nausea and vomiting; ICU, intensive care unit; PCIA, patient-controlled intravenous analgesia; SD, standard deviation; PSM, propensity score matching.

[§]Viral hepatitis includes HBV and HCV infection.

*Crystalloid fluid means lactated Ringer's solution and colloid fluid means hydroxyethyl starch solution (Voluven) in the studied center.

[§§]NSAIDs means flurbiprofen axetil in the studied center.

[§§§] The body temperature is reflected by the armpit temperature. Severe PONV is defined as episodes of expulsion of gastric contents that need antiemetic treatment.

With the development of surgical techniques and perioperative management, resection of hepatic tumors has been one of the most popular choices for patients with HCC (2018). The application of the occlusion of portal triad and total vascular exclusion minimizes intraoperative blood loss and the need for blood transfusion (4, 20). Nonetheless, both techniques cause inevitable IRI that may impair liver function and regeneration after hepatectomy. Furthermore, surgical trauma and stress response, excessive inflammatory response, and poor liver conditions with hepatitis or cirrhosis cause heavy burden on the liver (21). Therefore, perioperative protection of the liver is of significant concern for patients undergoing hepatectomy (22).

Numerous strategies have been designed for reducing liver injury and postoperative inflammatory response, and preserving liver function during hepatectomy (23, 24). For instance, studies have suggested that remote ischemia preconditioning (RIPC) could effectively reduce hepatic IRI after liver resection. In a randomized controlled trial (RCT) (23), our team investigated the effects of RIPC on hepatic IRI in patients undergoing liver resection (23). It was observed that the serum levels of ALT and AST were significantly decreased in the RIPC group compared to those in the control group. Second, some promising drugs such as ulinastatin and oxygen radical scavengers have been used for

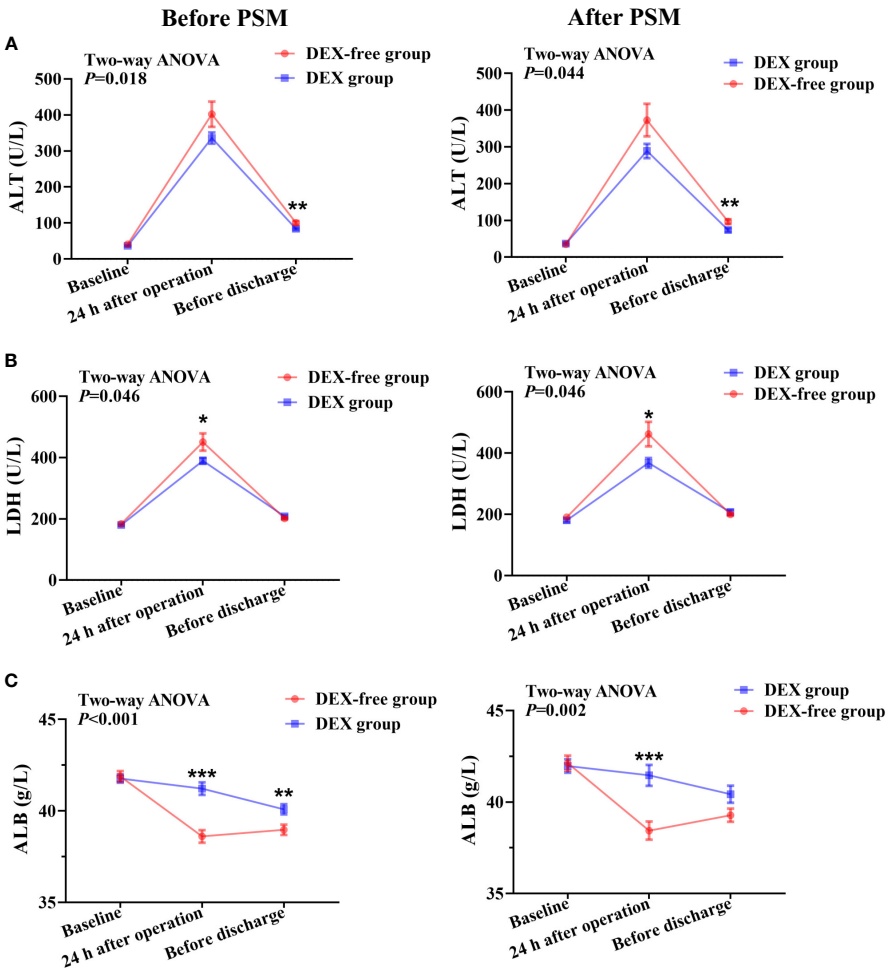

FIGURE 2
Serum levels of biomarkers of liver function at various time points in patients undergoing hepatectomy before and after PSM. **(A)**, serum ALT levels; **(B)**, serum LDH levels; **(C)**, serum ALB levels. Data were expressed as mean ± standard error. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

inhibiting inflammatory responses and oxidative stress (25, 26). However, their clinical application and validation are rarely reported and require more evidence.

DEX, a widely used sedative during surgery, was approved for sedation and analgesia by the United States Drug and Food Administration in 1999 (7). Owing to its excellent advantages of sedation, analgesia, antianxiety, inhibition of sympathetic nervous excitation, cardiovascular stabilization, and prevention of postoperative delirium, DEX has been widely used in clinical anesthesia and the ICU (8, 10, 27, 28). The contraindications of DEX mainly include 1) patients allergic to DEX, 2) pregnant, lactating women, and patients with severe heart block. Interestingly, numerous basic studies have also shown that DEX exerts strong multiorgan protective effects, including the liver, lung, heart, kidney, brain, and intestinal tract (5, 29, 30). These exciting findings prompt a series of clinical investigations. A meta-analysis discussed the effects of DEX on attenuating one-lung ventilation-associated lung injury by reviewing 20 clinical trials (31). The results suggested that perioperative administration of DEX could attenuate inflammation and ameliorate pulmonary oxygenation. Another meta-analysis reported that perioperative DEX infusion inhibited the release of epinephrine, norepinephrine, and cortisol and decreased the levels of blood glucose, interleukin (IL)-6, tumor necrosis factor-α (TNF-α), and CRP (5). In addition, the immune function was improved (5, 28, 32). Li et al. (27) also systematically reviewed the anti-inflammatory effects of perioperative DEX administration as an adjunct to general anesthesia in 15 clinical trials and reported significant decreases in the serum levels of IL-6, IL-8, and TNF-α after DEX use.

Several clinical studies have also explored the effects of DEX on liver protection (15, 16, 29). In an RCT conducted by Wang et al., perioperative administration of DEX was found to attenuate intestinal and hepatic injury in patients undergoing elective liver resection with inflow occlusion with no potential risk (15). In another RCT conducted by Zhang et al., the concentrations of α-glutathione S-transferase, IL-6, TNF-α, ALT, and AST were found to be significantly lower in the DEX group than in the control group (6). Nevertheless, the sample sizes of these studies were relatively small (n = 22–29 per group). In our study, we included 494 patients for analysis in total. Protective effects of DEX on the liver along with a decrease in the serum levels of ALT and LDH in the DEX group

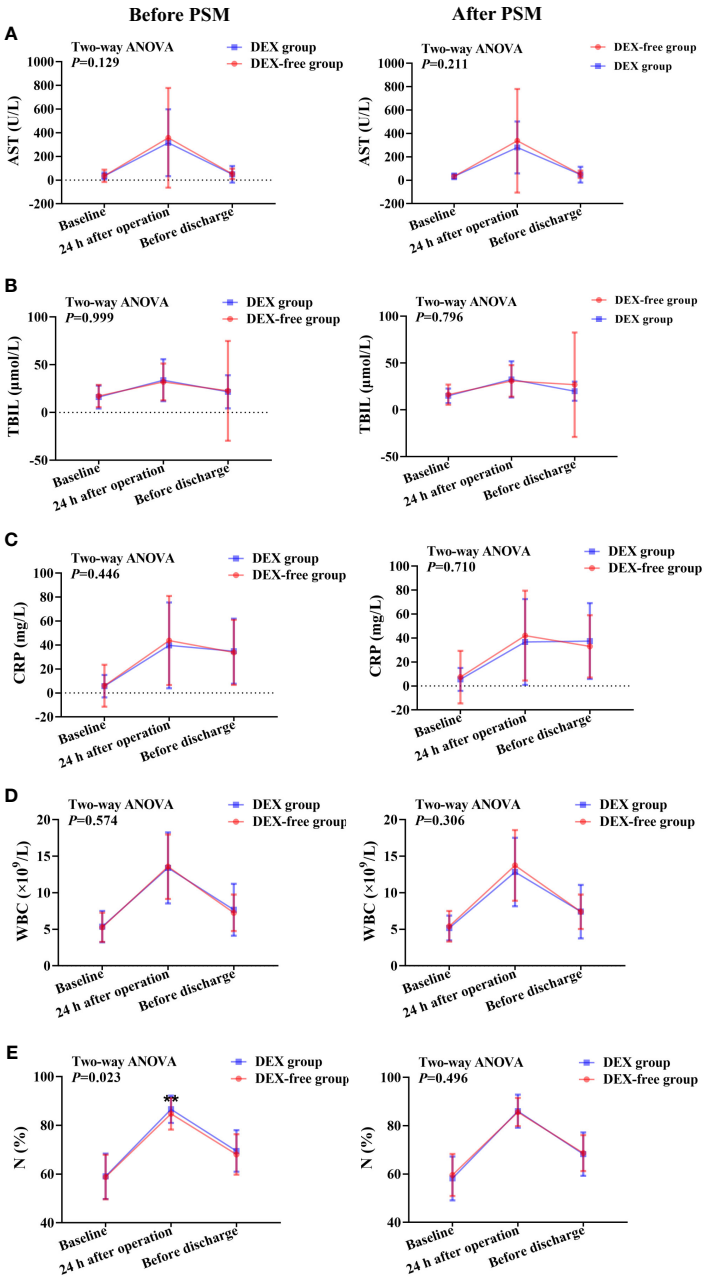

FIGURE 3
Expression levels of biomarkers of liver function and inflammation at various time points in patients undergoing hepatectomy before and after PSM. **(A)**, serum AST levels; **(B)**, serum TBIL levels; **(C)**, serum CRP levels; **(D)**, peripheral WBC count; **(E)**, percentage of neutrophils (N%) in peripheral blood. Data were expressed as mean ± standard deviation. **, $P < 0.01$.

were observed, compared to those in the DEX-free group. Interestingly, our results also suggested that the ALB level was significantly higher at 24h after surgery in the DEX group, which had not been reported previously in the case of hepatectomy. It appears that DEX could maintain the productive function of the liver as well. These findings support the use of DEX for reducing liver injury and maintaining ALB production in hepatectomy, which may bring significant improvement of liver function for patients. However, no differences in the levels of inflammation biomarkers such as serum CRP, WBC, and N% in peripheral blood between the two groups were found, indicating that DEX may exerted limited effects on early postoperative inflammatory responses.

The potential mechanism of action of DEX in alleviating liver injury involves multiple aspects such as anti-inflammatory and anti-IRI effects (33, 34), inhibition of hepatocyte apoptosis (35, 36), promotion of liver regeneration (9), regulation of immune function, and attenuation of oxidative stress (13, 35, 37). For instance, Zhang et al. reported that DEX could alleviate hepatic injury following intestinal IRI *in vivo* and *vitro* by upregulating β-catenin expression (34). Zhao et al. found that DEX alleviated hepatic injury by

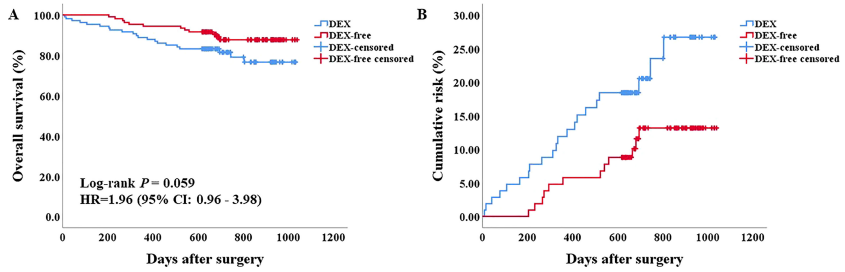

FIGURE 4
Survival analysis of patients after PSM. **(A)** the Kaplan–Meier survival curve of patients in the two groups. **(B)** the cumulative risk of patients in the two groups.

TABLE 3 Univariable and multivariable Cox regression model analysis of OS in patients after PSM.

Independent predictive factor	Univariable Cox analysis			Multiple Cox analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
DEX usage						
DEX-free	1	0.96-3.98	0.059	1	0.93-4.29	0.076
DEX	1.96			2.00		
Drinking						
No	1	1.02-4.00	0.045	1	1.05-4.78	0.038
Yes	2.02			2.23		
PVTT						
No	1	2.45-14.86	0.000	1	1.49-10.12	0.005
Yes	6.04			3.89		
Tumor size*						
< 3 cm	1	1.13-3.17	0.015	1	1.01-4.27	0.048
≥ 3 cm	1.89			2.07		
Hepatic inflow occlusion						
No	1	0.24-0.96	0.039	1	0.24-1.27	0.165
Yes	0.48			0.56		
Plasma or RBC transfusion						
No	1	1.07-4.75	0.032	1	0.62-3.79	0.358
Yes	2.26			1.53		

OS, overall survival; DEX, dexmedetomidine; HR, hazard ratio; CI, confidence interval; PVTT, portal vein tumor thrombus; RBC, red blood cell; PSM, propensity score matching.
* Tumor size is defined as the maximum diameter of tumor or the sum of maximum diameter when tumor number exceeds one.

inhibiting oxidative stress and activating the Nrf2/HO-1 signaling pathway *in vitro* (13). Other potential signaling pathways that are regulated by DEX include TLR4/MyD88/NF-κB, GSK-3β/MKP-1/Nrf2, and PI3K/AKT (35, 38, 39). Studies have also shown that miRNA and LncRNA were regulated by DEX (36, 40, 41).

Regarding the effect of DEX on cancer biology, it still remains unclear and controversial (41–44). Basic and clinical studies have suggested that DEX could regulate the malignancy of cancer cells and influence the prognosis of patients, but the conclusions are conflicting (41, 44, 45). Though significant decrease in OS was found in the DEX group compared with the DEX-free group only before PSM, the difference disappeared after PSM. Therefore, it is hard to draw conclusions regarding the effects of DEX on the prognosis of patients with HCC based on the present findings, and therefore further well-designed, large sample size, prospective studies are required to explore the effects of DEX on the malignance of cancer cells. Considering the possible adverse effects of DEX on the long-term prognosis of patients with HCC, we should balance the benefits and harm of DEX for patients undergoing hepatectomy.

This study has several limitations. First, it is a single-center retrospective study, and a multicenter or a prospective cohort study with a larger sample size would elevate the reliability of our findings. Second, the duration of protective effects induced by DEX is unclear, and more investigative time points are necessary. Third, examination of more liver function and inflammation biomarkers may help us understand the effects of DEX on liver function and inflammatory response in a more comprehensive manner.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by This study was approved by the Eastern Hepatobiliary Surgery Hospital's Institutional Review Board (Number: EHBHKY2021-K-011). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization, XW, YSu and JT. Methodology, XW, BQ and Y-RL. Software, XW and JL. Validation, YSh, ZP and YSu. Formal analysis, XW, ZP and FW. Investigation, JT. Resources, XW, XL and YL. Data curation, XW, YZ and XL. Writing—original draft preparation, XW and YSh; writing—review and editing, ZP and JT; supervision, JT. Funding acquisition, YSu, ZP, BQ and JT. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1108559/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Survival analysis of patients before PSM. **(A)**, the Kaplan–Meier survival curve of patients in the two groups. **(B)**, the cumulative risk of patients in the two groups.

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Case report and literature review: Isolated HCC- recurrence in gallbladder after curative resection

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Background: Liver resection (LR) is considered the mainstay treatment for eligible patients with hepatocellular carcinoma (HCC) and provides a 5-year overall survival (OS) of 60%–80%. However, the recurrence rate within five years after LR remains high, ranging from 40% to 70%. Recurrence in gallbladder after liver resection is extremely rare. Here, we present a case of isolated recurrence in gallbladder after curative resection of HCC and review the relevant literature. No similar cases have been reported before.
Case presentation: A 55-year-old male patient was diagnosed with HCC in 2009 and subsequently underwent a right posterior sectionectomy of the liver. In 2015, the patient underwent liver tumor radiofrequency ablation and three transarterial chemoembolization (TACE) procedures in succession for HCC recurrence. In 2019, a gallbladder lesion was detected by computed tomography (CT) without perceivable intrahepatic focus. We performed an *en bloc* resection of the gallbladder and hepatic segment IVb. The pathological biopsy suggested that the gallbladder tumor was moderately differentiated HCC. The patient survived more than 3 years in good condition, and there were no signs of tumor recurrence.
Conclusions: In patients with isolated gallbladder metastasis, if the lesion can be resected *en bloc* without remnants, surgery should be the preferred option. Both postoperative molecularly targeted drugs and immunotherapy are expected to improve the long-term prognosis.

KEYWORDS
liver resection, hepatocellular carcinoma (HCC), recurrence, gallbladder (GB) mass, metastasis

Introduction

Primary liver cancer ranks sixth in terms of incidence and is the third most common cause of cancer-related mortality worldwide (1). Hepatocellular carcinoma (HCC) accounts for 80% of all forms of liver cancer cases, followed by intrahepatic cholangiocarcinoma (iCCA) (14.9%) and other specified histology (5.1%) (2). HCC is a highly malignant disease (3). Liver resection (LR) is considered the mainstay of curative treatment for eligible patients with HCC and provides a 5-year overall survival (OS) of 60%–80%. However, the recurrence rate within five years after LR remains high, ranging from 40% to 70% (4). It has been reported that intrahepatic recurrence accounts for 66% of relapse cases, while extrahepatic recurrence accounts for 33% (5). Even in advanced HCC tumors, intrahepatic recurrence remains predominant (6–8). Gallbladder metastasis from HCC is a rare clinical occurrence. Autopsy studies report the frequency of

gallbladder metastasis as approximately 1.8%–5.8% (9–11). So far, there is still no consensus in the world about the treatment of this rare condition. We underwent a comprehensive review of relevant literature, and only 21 cases of intrahepatic HCC with gallbladder lesions presented synchronously or metachronously have been reported. All of these cases are summarized in Table 1.

The vast majority of cases were found at the time of routine concomitant gallbladder pathological examination after hepatectomy. Gallbladder lesions were found in only 4 cases during post-treatment follow-up after the primary liver tumors had been managed for 1–3 years. The initial treatment methods in all of these 4 cases are TACE and/or RFA. Since no case of isolated gallbladder recurrence after curative resection of HCC has been reported to date, we document this extremely rare case.

Case presentation

In our case report, a 55-year-old male patient was admitted to our department for recurrent pain in the upper-middle abdomen, which had started 2 years earlier and was aggravated with jaundice for 3 days. The patient complained of pain and discomfort that often radiated to the back and was accompanied by nausea and vomiting. Three days before admission, the pain flared up again, chills and fever were accompanied, and jaundice followed. The patient's prior medical history is as follows. In 2009, he received right posterior sectionectomy for primary liver cancer. In 2015, he received TACE and radiofrequency ablation for the treatment of recurrent HCC. In the meantime he took Sorafenib for one year. (Figure 1). Physical examination showed that the patient had skin and scleral jaundice and tenderness in the right upper quadrant. Laboratory tests indicated the following: white blood cell count (WBC) 16.47×10^9/L, neutrophil ratio (NEUR) 94.9%; albumin (ALB) 37.1 g/L, total bilirubin (TB) 125.7 μmol/L, direct bilirubin (DB) 72.9 μmol/L, aspartate aminotransferase (AST) 111.5 U/L, alanine transferase (ALT) 355.8 U/L, gamma-glutamyltransferase (GGT) 289.1 U/L; serum α-fetoprotein (AFP) 401.23 ng/ml; prothrombin time (PT) 18.8 s, prothrombin time international normalized ratio (PT-INR) 1.64; procalcitonin (PCT) 4.77 ng/ml, and interleukin-6 (IL-6) 201.5 pg/ml. Hepatitis B surface antigen and hepatitis C virus antibody were negative. An abdominal computed tomography (CT) scan showed that the lesion filled the gallbladder cavity. The wall of the lower segment of the common bile duct was thickened. Liver cirrhosis was also revealed. This gallbladder tumor showed punctate enhancement in the hepatic arterial phase and then became less dense than the liver parenchyma in the portal phase (Figure 2). No regional lymph nodes were enlarged.

The preoperative diagnosis was considered gallbladder tumor with acute cholangitis, which was potentially malignant. Therefore, hepatectomy of segment IVb, cholecystectomy and common bile duct exploration were planned in this case. Intraoperative exploration revealed extensive intraperitoneal adhesions and gallbladder enlargement with dimensions of 12 cm × 4 cm × 3 cm. The gallbladder was solid and tough, while the liver was soft. Because there was no metastasis to the lymph nodes or peritoneum, we performed a monobloc resection of the gallbladder and hepatic segment IVb, and common biliary duct exploration was also performed. The frozen section of the intraoperative specimen indicated a malignant tumor (gallbladder lumen occupying) and probable metastasis of HCC. Subsequent biliary exploration found several stones in the lower part of the common bile duct. After the stones were removed, the lower part of the common bile duct was observed with a choledochoscope, and no tumor invasion or neoplasm was found. Macroscopically the diseased gallbladder appeared to be filled with white soft tumor tissue, and some tissue had extended along the cystic duct to the common bile duct (Figure 3A). The operative time was 360 min, and blood loss was 200 ml. The postoperative paraffin histopathology and immunohistochemistry showed a moderately differentiated HCC with necrosis (Figure 3B). The final diagnosis was amended to HCC recurrence in gallbladder, choledocholithiasis and acute cholangitis. Antibiotics and hepatoprotective drugs were used in postoperative management, and the patient recovered uneventfully within 10 days.

The follow-up showed that the patient was in good condition and survived more than 40 months with no signs of tumor recurrence. To date, the patient has not taken any targeted drugs and immunotherapy drugs we recommended for treatment after surgery. The patient refused the medication because of the significant side effects of sorafenib at the time of the first relapse.

HBV, hepatitis B virus; HCV, hepatitis C virus; Alc, alcoholic hepatitis; Mt, multiple tumors; St, single tumor; NA, not available; S, synchronous; M, metachronous; GBTT, gallbladder vein tumor thrombus; MIG, massive intragallbladder growth; mp, muscularis propria; m-mp, mucosal layer-muscle layer; sm, submucosal layer; Mod, moderate; mo, month.

Discussion

As the tributaries of the portal vein are vulnerable to the invasion of HCC, the prevalence of portal vein tumor thrombosis (PVTT) is widespread in advanced HCC patients. HCC cells can be shed from the original PVTT by the portal vein blood flow and disseminate to the distal or even proximal perfusion areas. Therefore, intrahepatic metastasis occurs frequently. In terms of gallbladder metastasis from HCC, Nakashima et al. proposed four possible pathways: (1) hematogenous metastasis through the portal venous system; (2) lymphatic metastasis; (3) direct invasion from adjacent liver parenchyma; and (4) peritoneal dissemination (11). The first pathway was considered the most likely route of HCC cell migration to the gallbladder. In patients with liver cirrhosis, the portal vein flow velocity is reduced compared with that of normal liver (26). Meanwhile, the incidence of bidirectional and reversed flow in the portal venous system in cirrhosis is 10.8% (27). Portal flow can even be occluded by occupation of the entire lumen by PVTT. Sugita et al. identified 72 cystic veins in 27 patients in their research and revealed that all cystic veins drained into the intrahepatic sinusoids or portal branches *via* the hepatic hilum (17 patients,

TABLE 1 Characteristics of metastatic hepatocellular carcinoma to the gallbladder.

Case	First author	Year	Age/ sex	Background	HCC			management	Synchronous	PVTT	Morphologic type	Histological type	Prognosis
					Location	Size (cm)	Number						
1	Terasaki (12)	1990	71/F	Non B non C	S2/3/4	NA	Mt	None	S	+	GBTT/MIG	NA	Soon died
2	Maruo (13)	1994	73/M	Non B non C	S4	4.8	St	Lt. hepatectomy	S	–	Elevated	Mod	32 mo alive
3	Nishida (14)	1997	48/M	HBV	S4/5	NA	Mt	Wedge resection of the gallbladder bed	S	+	Diffuse	Mod	NA
4	Lane (15)	2002	78/M	NA	Right Lobe	NA	Mt	Wedge resection of the gallbladder bed	S	NA	GBTT	Well	Died of pneumonia
5	Chiba (16)	2002	50/M	HCV	S5	5	St	anticancer agents	S	+	GBTT/MIG	Mod	6 mo dead
6	Hwang (17)	2003	65/M	HBV	S4/8	4	Mt	TACE + cholecystectomy	M	NA	Polypoid mass	Poor	NA
7	Terashima (18)	2007	49/M	HBV	S5/6/7/8	10.7	Mt	TAC + cholecystectomy	M	+	Polypoid mass	Mod	13 mo alive
8	Ando (19)	2009	75/M	HCV	NA	NA	Mt	Wedge resection of the gallbladder bed	S	NA	Pedunculated	NA	NA
9	Murakami (20)	2010	53/M	HBV Alc	S7/8	14	Mt	Rt. hepatectomy	S	+	GBTT	Poor	63 mo alive
10			61/M	HCV	S5/8	9.5	Mt	Rt. hepatectomy	S	+	GBTT	Poor	4 mo alive
11			79/M	Alc	S2/3/4	13	Mt	Rt. hepatectomy	S	+	GBTT	Mod	6 mo dead
12			47/M	HBV	S4	6.5	Mt	Rt. hepatectomy	S	+	NA (mp)	Poor	54 mo dead
13			47/M	HBV	S2/3/4	13	Mt	Rt. hepatectomy	S	+	NA (mp)	Poor	9 mo dead
14			32/M	HBV Alc	S5/6/7/8	15	Mt	Rt. hepatectomy	S	+	NA (mp)	Poor	3 mo dead
15			74/M	HCV	S5/6	5	St	Rt. hepatectomy	S	+	NA (sm)	Poor	5 mo dead
16			66/M	Alc	S5/8	3.5	Mt	Rt. anterior sectionectomy	S	+	Protruding (m-mp)	Poor	6 mo dead
17	Monden (21)	2011	66/M	HCV	S5/8/	NA	St	TAC + RFA + cholecystectomy	M	–	Elevated + diffuse	Mod	10 mo alive
18	Kanzaki (22)	2011	48/F	Non B non C	S5	1.3	St	Wedge resection of the gallbladder bed	S	–	Below serosa	Mod	24 mo alive
19	Wakasugi (23)	2012	74/M	HCV	S1/5/6/7/8	8.8	Mt	Wedge resection of the gallbladder bed	S	+	GBTT	Poor	2 mo dead
20	Choi (24)	2012	62/M	NA	S2/4/5/8	NA	Mt	TACE + cholecystectomy	M	NA	Polypoid mass	Poor	NA
21	Hanazawa (25)	2021	66/F	Non B non C	S5/6/7/8	12	St	Rt. trisectionectomy	S	+	MIG	Poor	42 mo alive
22	Present case	2022	55/M	Non B non C	S4/7/8	NA	Mt	TACE + Wedge resection of the gallbladder bed	M	–	MIG	Mod	40 mo alive

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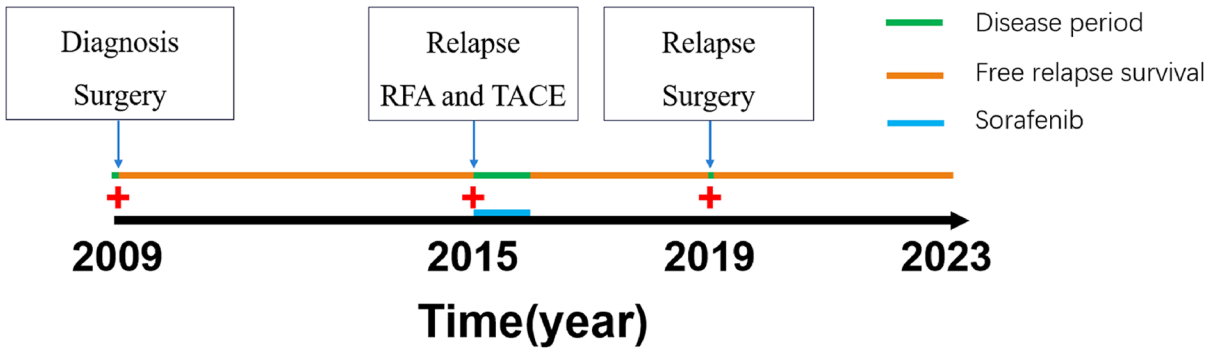

FIGURE 1
The timeline of patient's history.

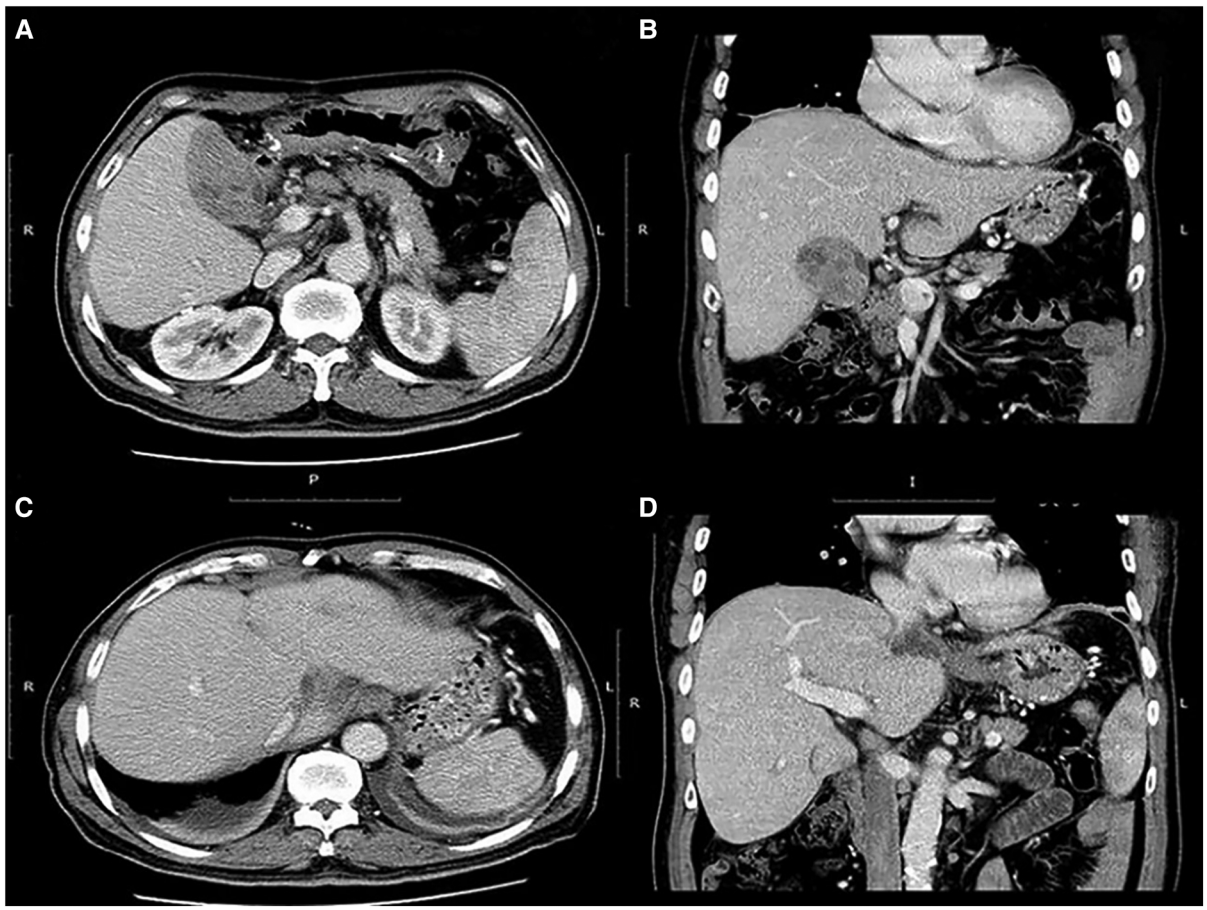

FIGURE 2
(A) computed tomography (CT) depicted a gallbladder tumor with dimensions of 8 × 4 cm. (B) Coronal image shows a clear demarcation between the tumor and the adjacent liver parenchyma. (C) No perceivable intrahepatic foci were found. (D) The right portal vein is tumor thrombus free.

21 veins) and hepatic bed (23 patients, 51 veins) (28). The portal branches and sinusoids in subsegment 4b and segment 5 are usually involved in the drainage of the cystic vein. Under these conditions, retrograde movement of HCC cells is possible, which may result in tumor invasion along the gallbladder vein into the gallbladder lumen. The above anatomic features of the cystic vein coincide with the occurrence site of HCC in the liver. In 19 out of 22 cases, the HCC tumor was located in segment 4 and/or segment 5, one case's location was not available, and one case was located in segment 7/8. PVTT was encountered in 14 cases. Histopathological examination confirmed the presence of gallbladder vein tumor thrombosis (GBTT) in 7 cases. Murakami

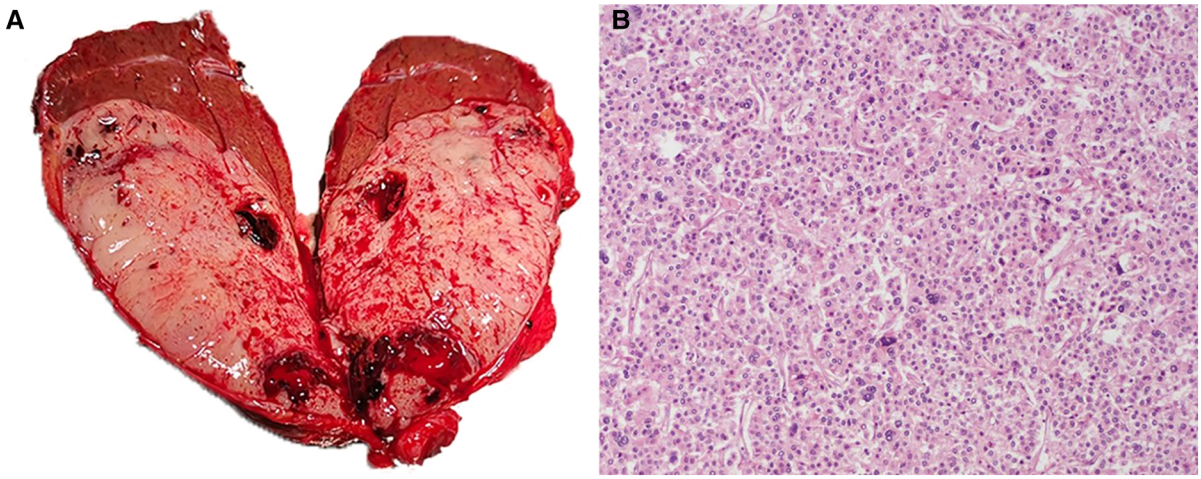

FIGURE 3
(A) macroscopic examination shows that the gallbladder lumen is filled with white fish-like tissue. (B) Histopathological examination revealed moderately differentiated hepatocellular carcinoma cells (hematoxylin and eosin, × 100).

et al. defined "metastasis" through the cystic vein as "local extension", which is a more appropriate description of this hematogenous route of gallbladder spread (20).

In terms of this particular case, preoperative differential diagnosis of primary gallbladder carcinoma and gallbladder metastasis from HCC is difficult due to the lack of typical imaging features. HCC only rarely breaks through the muscle layer and collagen fibers of the gallbladder wall, whereas gallbladder carcinoma can easily infiltrate the liver (16). All cases we reviewed were confirmed as metastasis by postoperative histopathological examination of the resected specimen. This patient's liver cancer first arose in the right posterior lobe of the liver in 2009, which is not close to the gallbladder bed, but recurrence occurred several times after surgery with tumors located in segment 4. HCC cells may migrate from recurrent lesions through the branches or sinusoids between the cystic vein and the portal vein. The pathological features were also similar to those of several other metachronous cases. Metachronous gallbladder tumors are mainly characterized by polypoid growth in the gallbladder lumen and are often detected by CT, whereas synchronous gallbladder tumors are usually found by postoperative pathological examination and are often characterized by the presence of gallbladder vein tumor thrombus (GBTT). Once extrahepatic metastasis of liver cancer occurs, the prognosis of surgical resection is often poor. Uchino et al. reported that the 1-year survival rate was 39.3%, and the 3-year and 5-year survival rates were 7.4% and 4%, respectively (8).

However, we noticed that the recurrent tumor in this case mainly grew in the gallbladder lumen and entered the common bile duct, causing biliary obstruction instead of invading the gallbladder muscular layer and serosa. The same phenomenon was also found in other cases. This indicates that recurrent gallbladder tumors are more inclined to follow the growth pattern of primary hepatocellular cancer, such as growing toward areas of lower pressure, including veins and bile ducts, to form a tumor thrombus. Primary gallbladder cancer, meanwhile, tends to grow more aggressively by infiltrating the gallbladder wall (16).

Secondary HCC is often classified as multicentric carcinogenesis (MC), intrahepatic metastasis (IM), and extrahepatic metastasis. Previous studies have suggested that early recurrences (≤1 year after primary lesion resection) appear to arise mainly from IM, whereas late recurrences (>1 year after primary lesion resection) are more likely to be the result of MC (29). Arii et al. showed that patients with extrahepatic metastasis originating from MC had a significantly better outcome than those originating from IM (29). In the current study, the patient's primary lesion that appeared in 2009 was surgically removed. Multiple intrahepatic recurrences that occurred in 2013 were cured with local treatment. As the patient had been disease free for 4 years prior to recurrence, the recurrences can be considered the result of MC. In terms of extrahepatic metastases, Yang et al. divided extrahepatic metastases after liver resection into three types. Pattern I: first recurrence in the liver followed by spread outside the liver after repetitive intrahepatic recurrences and repetitive locoregional treatments, pattern II: intrahepatic and extrahepatic recurrences exist simultaneously, and pattern III: extrahepatic recurrence without intrahepatic lesions at first recurrence (30). According to their study, pattern I was significantly better than pattern II in terms of overall survival and disease-free survival rates. This case corresponds exactly to pattern 1, with repetitive intrahepatic recurrences after resection of the primary liver tumor and finally development of isolated gallbladder metastasis. After wedge resection of the gallbladder bed and administration of an anticancer agent, the patient finally had a good prognosis.

There is no consensus on the management of extrahepatic metastasis. Surgical resection and antitumor agents are currently predominant in management. According to Murakami et al. (20) and Hanazawa et al. (25), favorable results were obtained using adjuvant therapy after resection of recurrent gallbladder tumors from HCC. This indicates that the outcomes of recurrent HCC

in gallbladder undergoing radical resection are better than those of primary gallbladder cancer. Therefore, for patients with isolated recurrent gallbladder tumors, if the lesion can be resected *en bloc* without remnants, surgical resection should be performed aggressively. Both postoperative molecularly targeted drugs and immunotherapy are expected to improve the survival rate and prognosis of patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

Conception and design of study are attributed to GC and PC. Acquisition of data is attributed to GYL and BZ. Collection of relevant articles is attributed to YM and SRZ. Data analysis, Drafting of manuscript and critical revision are attributed to SRZ. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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