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Advances in surgical treatment of hepatobiliary tumors

Edited by
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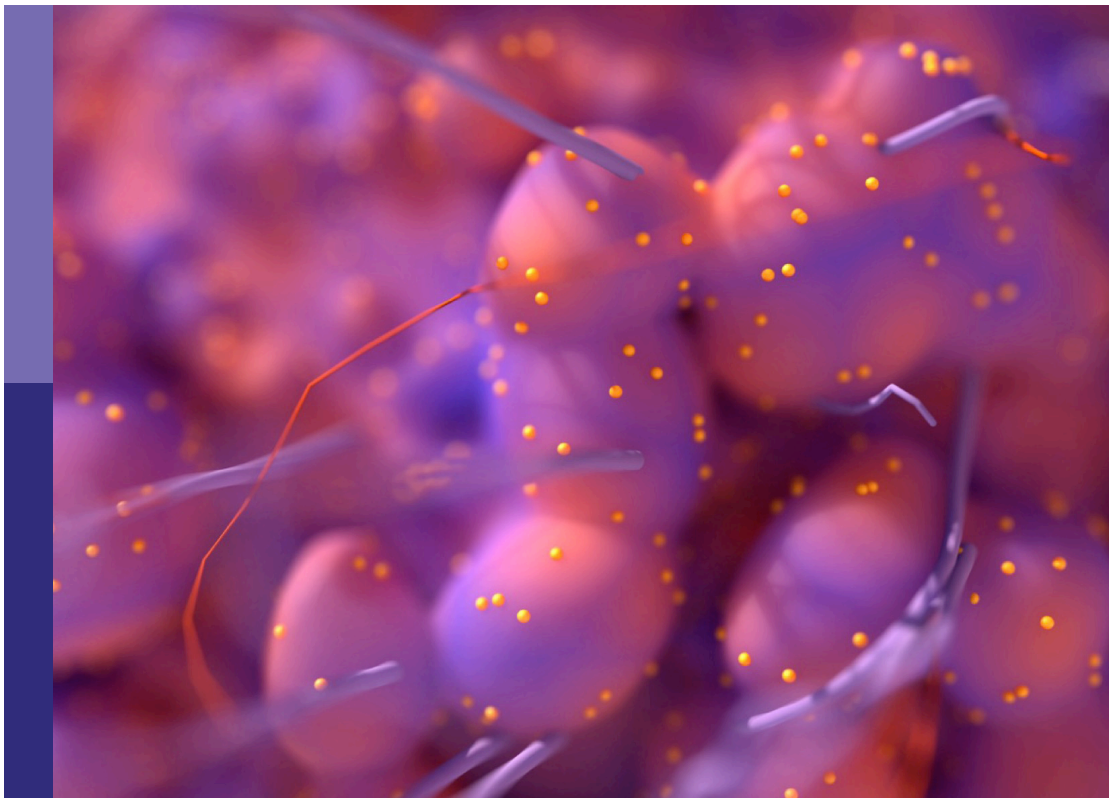

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Advances in surgical treatment of hepatobiliary tumors

Topic editors

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Table of contents

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ORIGINAL RESEARCH
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A Practical Nomogram and Risk Stratification System Predicting Cancer-Specific Survival for Hepatocellular Carcinoma Patients With Severe Liver Fibrosis

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Objective: Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths worldwide. This study aims to construct a novel practical nomogram and risk stratification system to predict cancer-specific survival (CSS) in HCC patients with severe liver fibrosis.

Methods: Data on 1,878 HCC patients with severe liver fibrosis in the period 1975 to 2017 were extracted from the Surveillance, Epidemiology, and End Results database (SEER). Patients were block-randomized (1,316 training cohort, 562 validation cohort) by setting random seed. Univariate and multivariate COX regression analyses were employed to select variables for the nomogram. The consistency index (C-index), the area under time-dependent receiver operating characteristic curve (time-dependent AUC), and calibration curves were used to evaluate the performance of the nomogram. Decision curve analysis (DCA), the C-index, the net reclassification index (NRI), and integrated discrimination improvement (IDI) were used to compare the nomogram with the AJCC tumor staging system. We also compared the risk stratification of the nomogram with the American Joint Committee on Cancer (AJCC) staging system.

Results: Seven variables were selected to establish the nomogram. The C-index (training cohort: 0.781, 95%CI: 0.767–0.793; validation cohort: 0.793, 95%CI = 95%CI: 0.779–0.798) and the time-dependent AUCs (the training cohort: the values of 1-, 3-, and 5 years were 0.845, 0.835, and 0.842, respectively; the validation cohort: the values of 1-, 3-, and 5 years were 0.861, 0.870, and 0.876, respectively) showed satisfactory discrimination. The calibration plots also revealed that the nomogram was consistent with the actual observations. NRI (training cohort: 1-, 2-, and 3-year CSS: 0.42, 0.61, and 0.67; validation cohort: 1-, 2-, and 3-year CSS: 0.26, 0.52, and 0.72) and IDI (training cohort: 1-, 3-, and 5-year CSS:0.16, 0.20, and 0.22; validation cohort: 1-, 3-, and 5-year CSS: 0.17, 0.26, and 0.30) indicated that the established nomogram

significantly outperformed the AJCC staging system ($P < 0.001$). Moreover, DCA also showed that the nomogram was more practical and had better recognition.

Conclusion: A nomogram for predicting CSS for HCC patients with severe liver fibrosis was established and validated, which provided a new system of risk stratification as a practical tool for individualized treatment and management.

Keywords: severe liver fibrosis, nomogram, cancer-specific survival, risk stratification system, hepatocellular carcinoma

INTRODUCTION

HCC is the second leading cause of cancer-related mortality globally and the fifth most severe malignancy (1, 2). The five-year survival rate for patients with HCC is low due to therapeutic restriction (3). The risk factors vary depending on the distribution of the region. For example, chronic hepatitis B virus infection is the primary factor in Asia, while chronic hepatitis C virus infection, alcoholic liver disease, and nonalcoholic fatty liver disease are the prominent risk factors in Europe and America (4–7). A total of 80%–90% HCC patients have biopsy evidence of liver fibrosis (8). Liver fibrosis, a chronic liver injury repair process, is characterized by the activation of hepatic stellate cells into myofibroblasts and the production of large amounts of extracellular matrix, leading to a gradual destruction of the normal structure and physiological function of liver tissue, with scar tissue replacing liver parenchyma and ultimately death, which may eventually lead to cirrhosis, liver failure, or liver cancer (9). Severe liver fibrosis is an irreversible biological process for which no drugs have been proven to be effective (10, 11). Moreover, the management of HCC patients with severe liver fibrosis is extremely controversial in nature (12).

The American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) system is the most commonly used method to evaluate the prognosis of patients with HCC (13). However, the TNM system has some limitations such as low accuracy, ignoring of other factors (age, sex, etc.), and poor performance in predicting individual survival risk (14). As a result, a new and personalized prediction model is needed to evaluate the prognosis of HCC patients.

Recently, clinical models related to nomograms have been widely applied for the survival prediction of tumor patients through a comprehensive analysis of neoplasm-related risk factors (15, 16). Moreover, nomograms can effectively predict tumor prognosis and promote personalized medicine. However, there are no prognostic models for HCC patients with severe fibrosis (Ishak 5–6; Advanced/severe fibrosis; METAVIR F4; Batt-Ludwig 4; Cirrhosis). Therefore, it is necessary to establish a practical, reliable, and specific prediction model to predict CSS for HCC patients with severe liver fibrosis.

METHODS

Data Collection

Clinically relevant data were extracted from the SEER database between 1975 and 2017 via SEER*Stat 8.3.9.2 software. The SEER database was made publicly accessible and private data for all patients were removed from the database, which indicated that institutional review board approval and informed consent were not required.

Collation of Data

The inclusion criteria were as follows: (a) HCC patients with severe liver fibrosis (Ishak 5–6; Advanced/severe fibrosis; METAVIR F4; Batt-Ludwig 4; Cirrhosis); (b) complete treatment information. The exclusion criteria were as follows: (a) unknown liver fibrosis score or mild liver fibrosis; (b) metastatic liver cancer; (c) imperfect treatment information; (d) unknown tumor stage; (e) unknown tumor pathological grade; (f) unknown household income; (g) other tumor death and unknown cause of death. Finally, eleven variables were included from the SEER database: age (at diagnosis), ethnicity, gender, tumor number, pathological grade, tumor size, extension, tumor stage (AJCC stage), type of surgery, AFP, and insurance. In addition, the seventh edition of the AJCC-TNM staging was used for the analysis.

Establishment of the nomogram

All patients were randomly divided into a training cohort and a validation cohort at a ratio of 7:3. The training cohort was used to create a nomogram, while the validation cohort was used for validation. Univariate and multivariate COX regression analyses were employed to obtain significant factors that significantly affected CSS and further construct the nomogram (**Supplementary Table**).

Validation of the Nomogram Model

C-index and ROC curves reflected the predictive capability of the nomogram. The value was above 0.5, indicating predictive performance, which could be divided into low precision (0.5–0.7), medium precision (0.71–0.9), and high precision (>0.9). 1-, 3-, and 5- year calibration curves were plotted to evaluate calibrating ability, and the 45-degree line was used as the actual outcome of the primary model.

Comparison of the Risk Stratification Associated with the Nomogram and AJCC

Based on the nomogram, a novel risk stratification system was developed, which could divide patients into low-, middle-, and high-risk groups (the best cut-off value for the total score was selected by using X-tile). The net reclassification index (NRI), C-index, IDI, and decision curve analysis (DCA) were adopted to compare the risk stratification of the nomogram model

with that of the AJCC stage system. The NRI, C-index, and integrated discrimination improvement (IDI) were applied to assess the improvement in risk prediction and determine the effectiveness of the new model. DCA was performed to evaluate the net benefit of various models. Kaplan–Meier curves were used to compare the risk stratification of the nomogram with that of AJCC staging criteria.

Data Analysis

Univariate and multivariate COX regression analyses, C-index, calibration curves, ROC curves, and DCA curves were generated using R version 4.1.2 and related software packages. The optimal cut-off point for risk stratification was selected utilizing X-tile (version 3.6.1). Statistical differences of distribution between the training and the validation cohorts were analyzed by the Chi-square test. All *p*-values resulted from two-side statistical testing, while a *p*-value less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 1,878 HCC patients with severe liver fibrosis were included in our study, with 1,316 (70%) in the training cohort and 562 (30%) in the validation cohort. The flow diagram is shown in **Figure 1**. Of all patients eligible for the study, there were 1,465 (77.82%) male patients and 413 female patients. There were 1,331 white and 243 black patients, which accounted for 71.14% and 12.99%, respectively. Of all the patients, 805 were treated conservatively and 300 were treated locally. A total of 394 patients underwent resection of liver masses and 379 underwent liver transplantation. A total of 1,539 patients were well-differentiated, while 339 were poorly differentiated. The baseline information related to the training and validation groups is provided in **Table 1**. There was no statistically significant difference between the two cohorts.

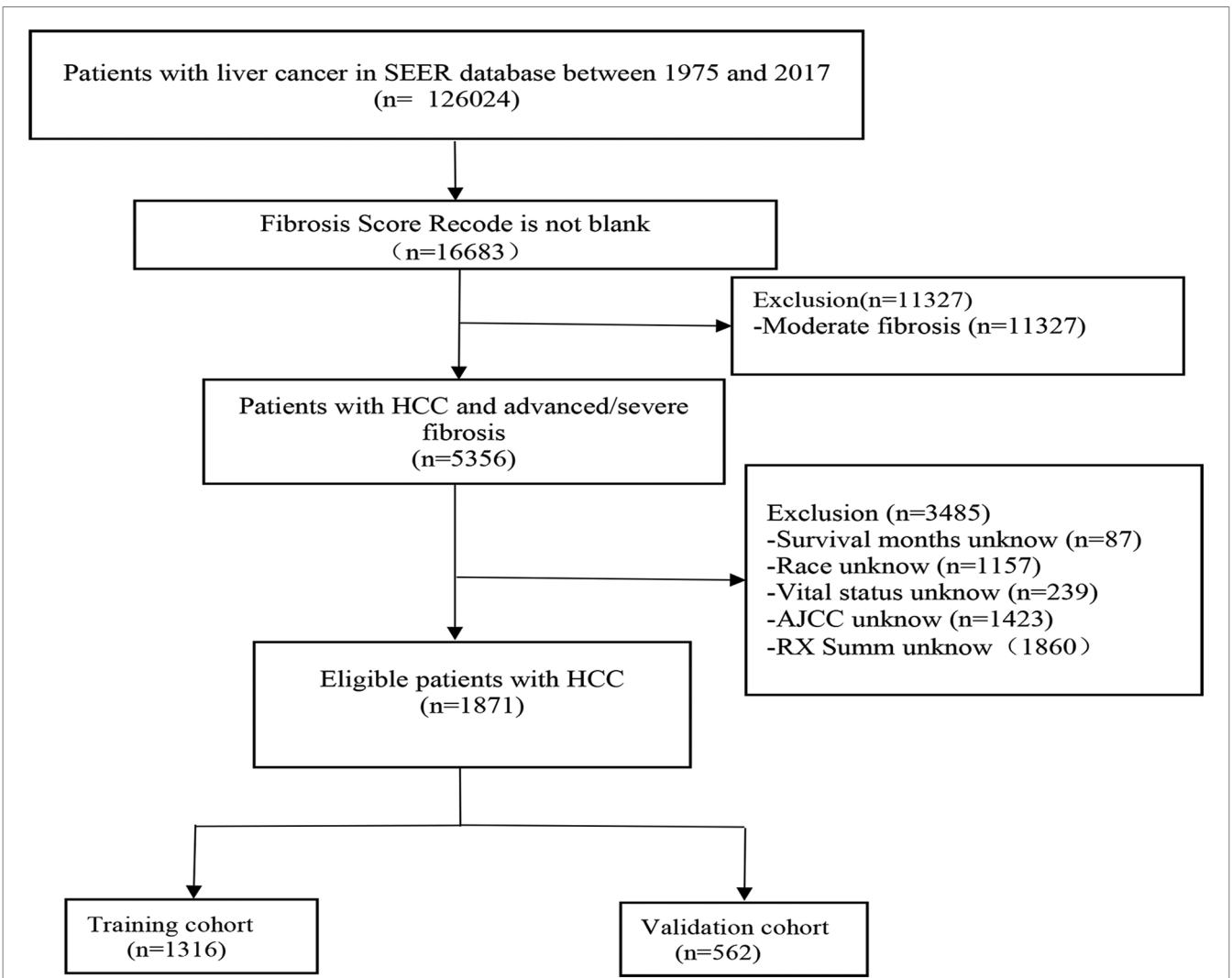

FIGURE 1 | Flow diagram of the hepatocellular carcinoma patients with severe liver fibrosis with training and validation cohorts.

TABLE 1 | Demographics and clinical characteristics of hepatocellular carcinoma patients with severe liver fibrosis at diagnosis.

Variable	Whole population		Training cohort		Validation cohort		*P* value
	N	%	*n*	%	*n*	%	
	1,871		1,316		562		
Age year							
<65	1,268	67.77	895	68.01	373	66.37	0.56
>65	610	32.60	421	31.99	189	33.63	
Race							
Black	243	12.99	171	12.99	72	12.81	0.16
White	1,331	71.14	945	71.81	386	68.68	
Other	304	16.25	200	15.20	104	18.51	
Sex							
F	413	22.07	290	22.04	123	21.89	0.78
M	1,456	77.82	1,026	77.96	439	78.11	
Grade							
Grade I and II	1,539	82.26	1,078	81.91	461	82.03	0.64
Grade III and IV	339	18.12	238	18.09	101	17.97	
AJCC stage[a]							
I	820	43.82	585	44.45	235	41.81	0.13
II	600	32.06	409	31.07	191	33.98	
III	301	16.08	217	16.48	84	14.94	
IV	45	2.40	105	7.97	52	9.25	
Size cm							
0–5	1,284	68.63	896	68.09	388	69.04	0.35
>5	594	31.75	420	31.91	174	30.96	
Number							
1	1,519	81.19	1,063	80.78	456	81.14	0.27
>1	359	19.19	253	19.22	106	18.86	
Extension							
Yes	375	20.04	249	18.92	436	77.58	0.61
No	1,503	80.33	1,067	81.08	126	22.42	
AFP							
Positive	1,286	68.73	899	68.31	387	68.86	
Negative	592	31.64	417	31.69	175	31.14	
Surgery							
No	805	43.03	580	44.07	225	40.04	0.22
Local treatment	300	16.03	210	15.96	90	16.01	
Hepatectomy	394	21.06	263	19.98	131	23.31	
Transplant	379	20.26	263	19.98	116	20.64	
Income[b]							
Low	1,028	54.94	700	53.19	328	58.36	0.35
High	850	45.43	616	46.81	234	41.64	

[a]*AJCC Stages: The seventh edition American Joint Committee on Cancer (AJCC) TNM staging system.*
[b]*Income: Low, annual income <6,499$, High, annual income ≥6,499$.*

Univariate and Multivariate COX Regression Analyses

Univariate COX regression analysis showed that age, race, pathological grade, AJCC stages, tumor size, AFP, surgery, tumor size, and income were all statistically significant on prognosis ($P < 0.05$) (**Table 2**). Multivariate analysis suggested that age, pathological grade, AJCC stages, AFP, surgery, and tumor size were independent prognostic factors affecting the CSS of HCC patients with severe liver fibrosis, which were, therefore, included in the nomogram model.

Construction and Validation of the Nomogram

Eventually, 7 variables (age, pathological grade, AJCC stages, tumor size, AFP, surgery, and income) were selected to construct the nomogram to predict the probability of CSS in HCC patients with severe liver fibrosis (**Figure 2**). First, risk scores for each variable were derived based on the information of patients. The total risk score of the patient is obtained by adding the scores of all variables, and the corresponding position of the risk score of the patient can be found in the line of total scores. Finally, the probability of 1-, 3-, and 5-year CSS for HCC patients with severe liver fibrosis could be referred by drawing a straight line on the last 3 rows. The C-indexes for the training and validation cohorts were 0.781 (95% CI: 0.767–0.793) and 0.793 (95% CI: 0.779–0.798) ($P < 0.05$), respectively. The calibration curve, ROC curve, and DCA curve are shown in **Figures 3–5**. The 1-, 3-, and 5-year time-dependent AUCs for the training cohort were 0.845, 0.835, and 0.842, respectively, while those for the validation cohort were 0.861, 0.870, and 0.876, respectively, manifesting that the model had excellent predictive performance. In addition, the nomogram-related DCA curves at 1, 3, and 5 years in the training and validation cohorts also exhibited promising potential for clinical application and better positive net benefits. The calibration curves revealed good consistency in the probability of 1-, 3-, and 5-year CSS between the nomogram prediction and the observed results in both cohorts.

Comparison of the Clinical Value of the Nomogram and AJCC Criteria

In the training cohort, the C-index of the nomogram was higher than that of the AJCC stage system (**Figure 6**). The NRIs for the 1-year, 3-year, and 5-year CSS were 0.42 (95% CI = 0.27–0.56), 0.61 (95% CI = 0.50–0.77) and 0.67 (95% CI = 0.49–0.80), respectively, in the training cohort, and 0.26 (95% CI = 0.17–0.46), 0.52 (95% CI = 0.22–0.76), and 0.72 (95% CI = 0.44–0.92), respectively, in the validation cohort. IDI (training cohort: 1-, 3-, and 5-year CSS: 0.16, 0.20, and 0.22; validation cohort: 1-, 3-, and 5-year CSS: 0.17, 0.26, and 0.30) indicated that the established nomogram significantly outperformed the AJCC staging system ($P < 0.05$) (**Table 3**). These results indicated that the nomogram was more accurate than predictions based on AJCC staging criteria. In addition, we compared the net benefit of the nomogram with the AJCC staging criteria. DCA curves in both the training and the validation cohorts showed that the nomogram better predicted 1-, 3-, and 5-year CSS because it added more net benefit compared with the AJCC staging criteria as well as the treat-all-patients scheme and the treat-none scheme.

TABLE 2 | The results of univariate and multivariate Cox regression analyses on variables for the prediction of CSS.

Character	Univariate		*P* Value	Multivariate		*P* Value
	HR	95%CI		HR	95%CI	
Age year						
<65	Reference			Reference		
>65	1.43	1.23–1.66	<0.001	1.24	1.06–1.45	<0.05
Race						
Black	Reference			Reference		
White	0.835	0.68–1.02	0.79	1.06	0.86–1.31	0.53
Other	0.67	0.51–0.88	0.003	0.88	0.66–1.17	0.38
Sex						
F	Reference			Reference		
M	1.19	1.00–1.43	0.04	1.03	0.86–1.24	0.68
Grade						
Grade I and II	Reference			Reference		
Grade III and IV	2.01	1.70–2.38	<0.001	1.57	1.31–1.87	<0.05
AJCC stage[a]						
I	Reference			Reference		
II	1.26	1.06–1.19	<0.001	1.41	1.17–1.70	<0.05
III	3.81	3.18–4.56	<0.001	1.46	1.15–1.85	<0.05
IV	5.02	3.37–7.47	<0.001	1.42	0.89–2.26	<0.05
Size cm						
0–5	Reference			Reference		
>5	1.28	1.14–1.54		1.21	1.17–1.46	<0.05
Number						
1	Reference			Reference		
>1	0.91	0.76–1.09	0.33	0.90	0.73–0.99	0.30
Extension						
No	Reference			Reference		
Yes	2.21	1.88–2.61	<0.001	1.28	1.05–1.58	<0.05
AFP						
Negative	Reference			Reference		
Positive	1.6	1.36–1.88	<0.001	1.19	1.01–1.41	<0.05
Surgery						
No	Reference			Reference		
Local treatment	0.35	0.29–0.44	<0.001	0.52	0.42–0.65	<0.05
Hepatectomy	0.33	0.27–0.40	<0.001	0.38	0.31–0.46	<0.05
Transplant	0.07	0.05–0.11	<0.001	0.11	0.07–0.14	<0.05
Income[b]						
Low	Reference			Reference		
High	0.8	0.69–0.92	0.03	0.85	0.73–0.99	<0.05

[a]*AJCC Stages: The seventh edition American Joint Committee on Cancer (AJCC) TNM staging system.*
[b]*Income: Low, annual income <6,499$, High, annual income ≥6,499$.*

Along with the generation of the nomogram, a risk stratification system, which was distinguished according to the calculation of the total score, was developed. All patients were classified into three risk groups: low risk (total score <446), middle risk (446 ≤ total score <504), and high risk (total score ≥504) (**Figure 7**). Kaplan–Meier curves presented clearly marked survival differences among patients in different risk groups. In contrast, the AJCC staging criteria model had limited ability to identify I–II and III–IV in both the training and the validation cohorts (**Figure 8**).

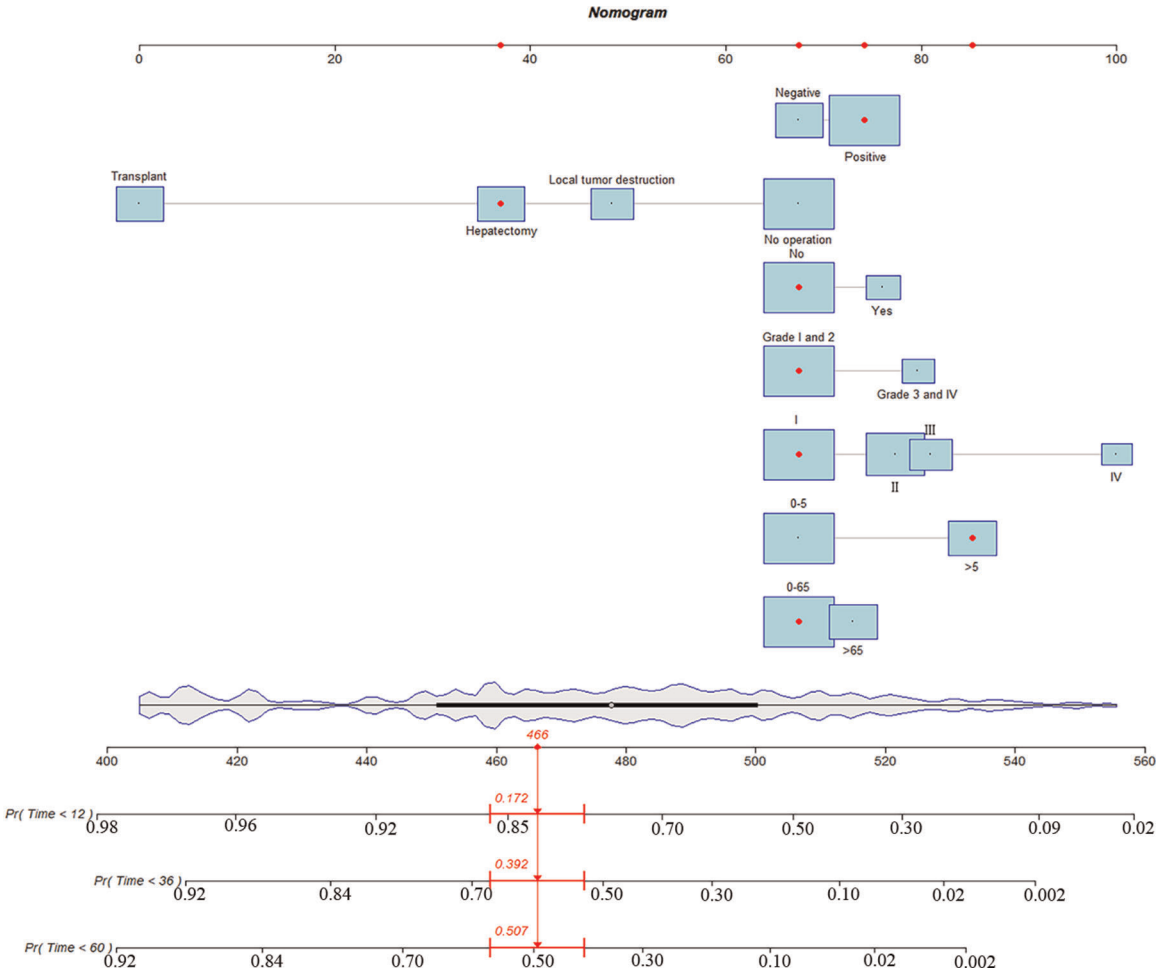

FIGURE 2 | A nomogram for hepatocellular carcinoma patients with severe liver fibrosis.

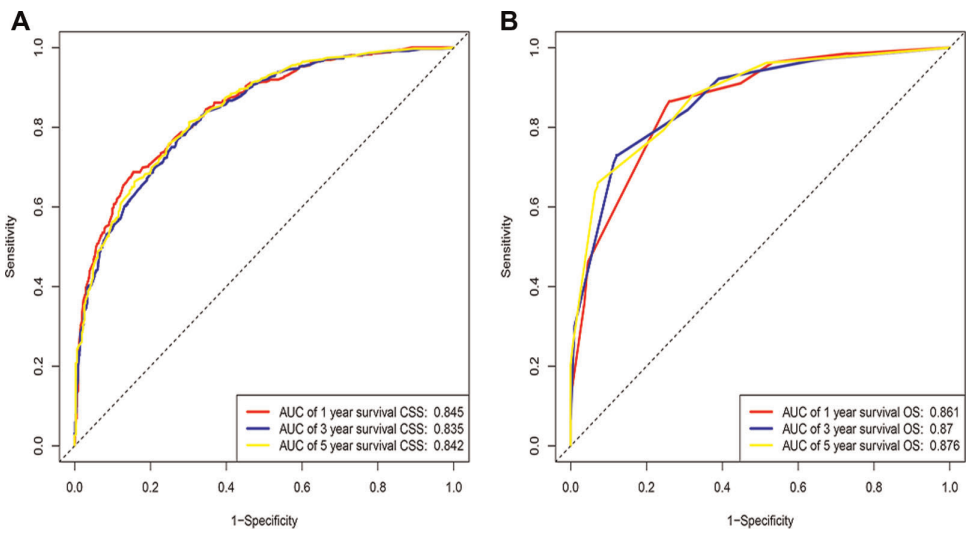

FIGURE 3 | ROC of the nomogram for 1-, 3-, and 5-year prediction. (**A**) Training cohorts based on the nomogram; (**B**) Validation cohorts based on the nomogram.

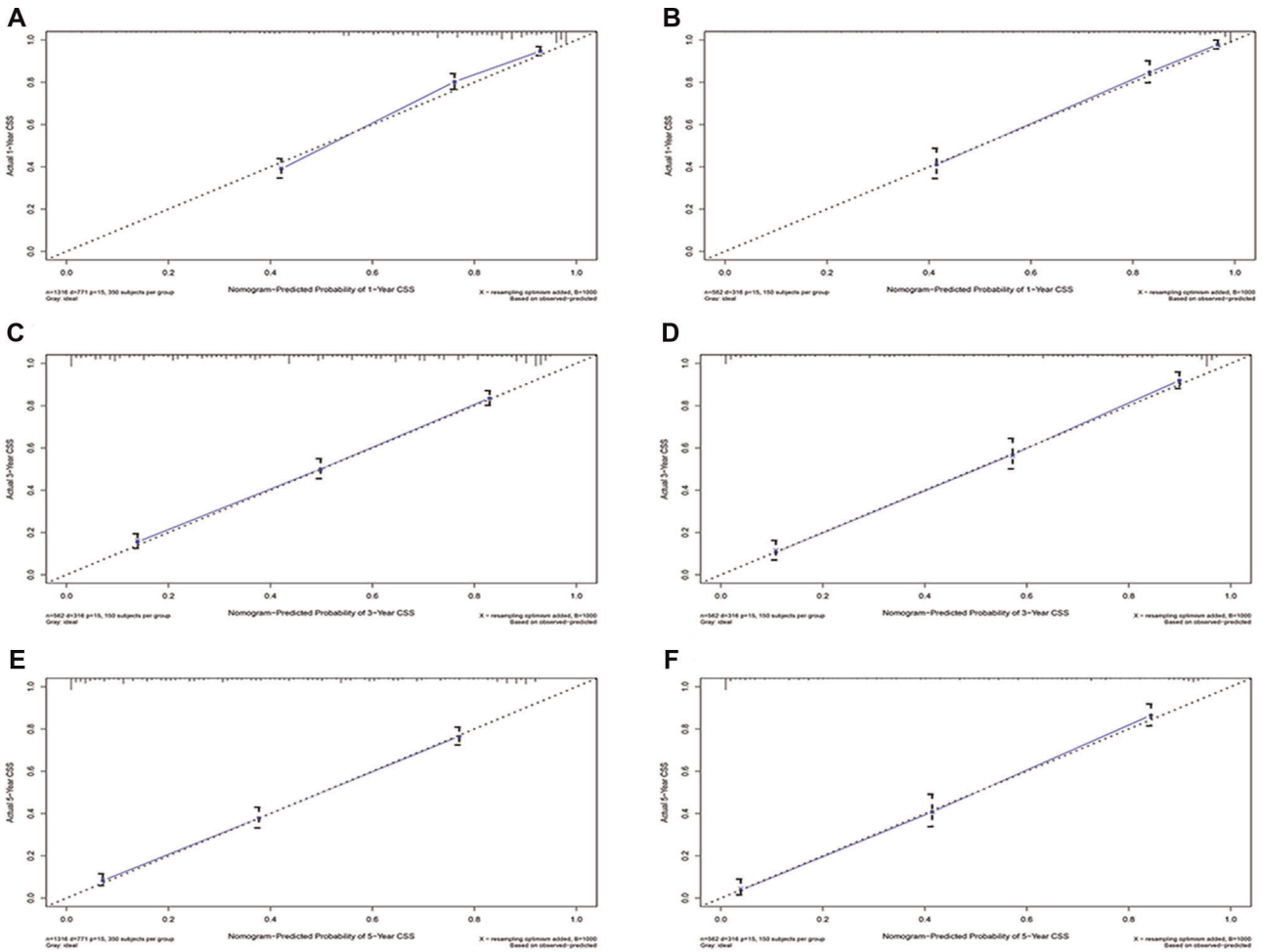

FIGURE 4 | Calibration plots of 1-year, 3-year, and 5-year CSS for hepatocellular carcinoma patients with severe liver fibrosis. (**A,C,E**) Calibration plot of 1-year, 3-year, and 5-year CSS in the training cohort; (**B,C,F**) Calibration plot of 1-year, 3-year, and 5-year CSS in the training cohort; CSS, cancer-specific survival.

DISCUSSION

HCC is the sixth most common malignant cancer in incidence worldwide (17, 18), with 80%–90% of patients suffering from liver damage, chronic inflammation, and fibrous repair (19). Findings have shown that fibroblasts secreting cytokines and growth hormones can implicitly or explicitly accelerate the value-added and invasion of HCC, while a proportion of tumor-associated fibroblasts is a part of the malignant microenvironment (20, 21). HCC, combined with severe liver fibrosis, has made clinicians face substantial challenges in therapy. Meanwhile, clinical evidence for the prognosis of HCC patients with serious liver fibrosis is scarce, and there is still a shortage of risk models. Consequently, this research developed and validated a nomogram to predict the prognostic value by analyzing the demographic and clinical characteristics of HCC patients with serious liver fibrosis in the SEER database. Multiple validation results indicated that the nomogram had favorable discriminatory ability. Based on the nomogram, we developed a novel risk stratification system where patients were classified into low-risk, middle-risk, and high-risk groups. Compared with the AJCC criteria, this risk stratification system not only accurately predicted the prognosis of patients, but also provided individualized management and treatment for HCC patients with serious liver fibrosis.

Age was an independent predictor for CSS in HCC patients with serious liver fibrosis, which indicated that older age was associated with poor prognosis. Multiple studies have shown that AJCC TNM stage is an independent influencing factor for HCC, which is generally consistent with our findings (22). Patients with a higher pathological grading have a longer CSS than those with a lower pathological grading, implying that pathological grading reflects the prognosis of HCC. AFP is one of the most relevant physiological markers for screening, clinical diagnosis, effectiveness evaluation, and post-treatment monitoring in high-risk populations of liver cancer. According to current studies (23), prediction models including serum AFP can enhance the predicting recurrence of tumor after liver transplantation.

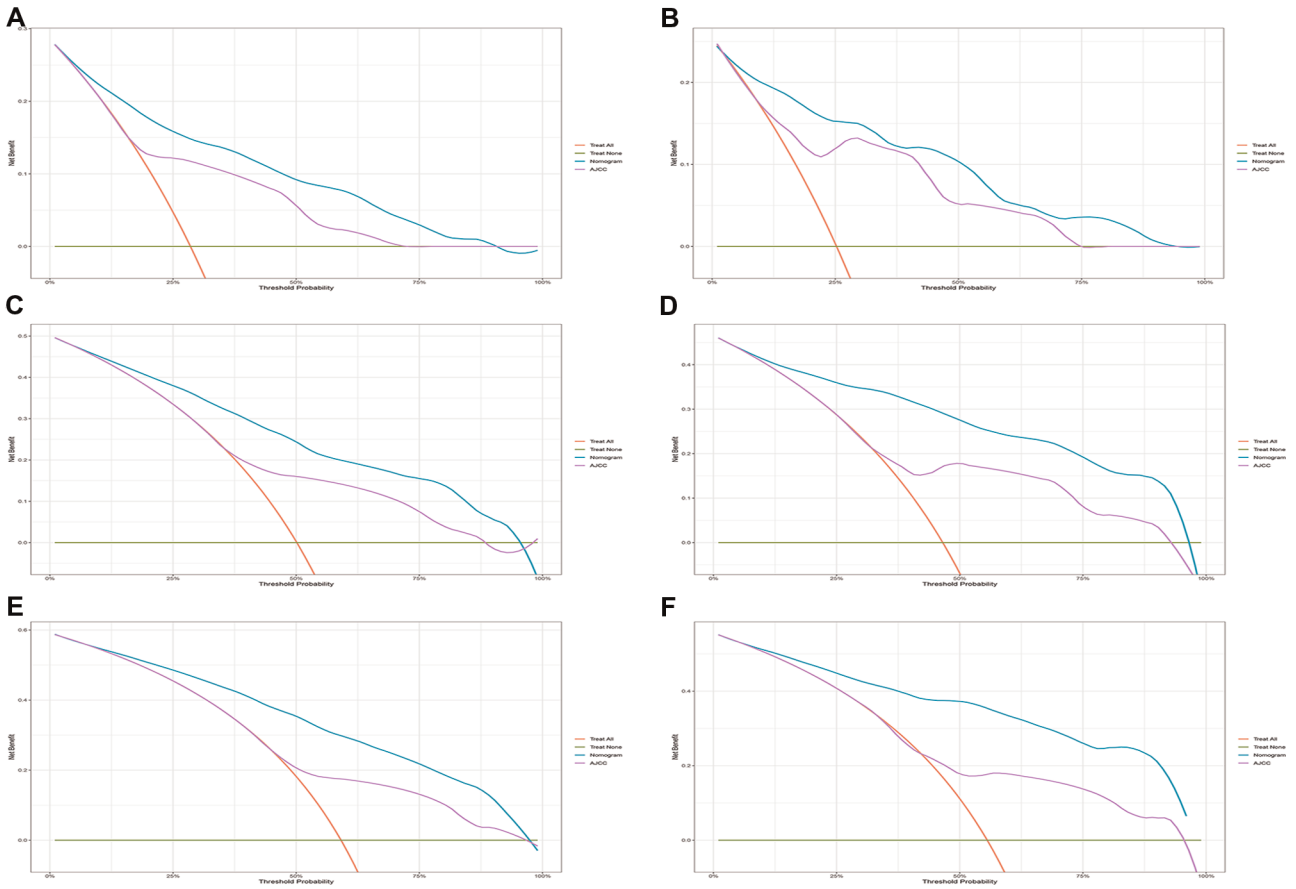

FIGURE 5 | Decision curve analysis. (**A,C,E**) DCA curve of 1-year, 3-year, and 5-year CSS in the training cohort; (**B,D,F**) DCA curve of 1-year, 3-year, and 5-year CSS in the validation cohort. DCA, decision curve analysis; CSS, cancer-specific survival.

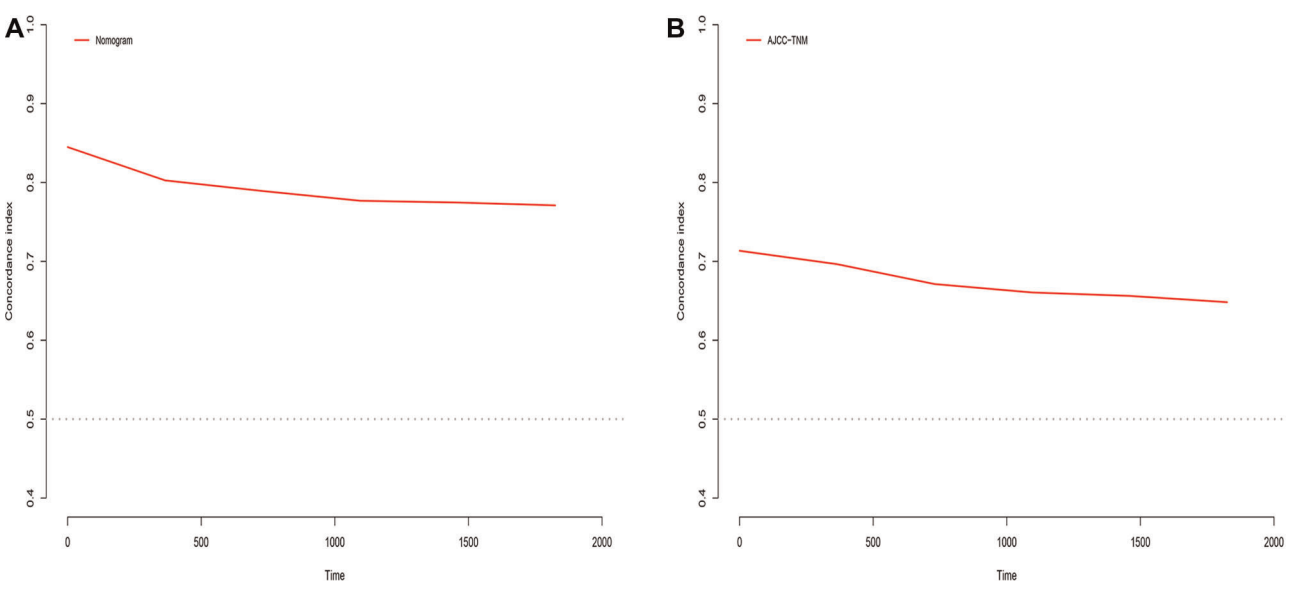

FIGURE 6 | C-index analysis. (**A**) The nomogram related C-index; (**B**) AJCC staging criteria related C-index.

TABLE 3 | NRI and IDI of the nomogram and AJCC staging criteria alone in CSS prediction for hepatocellular carcinoma patients with severe liver fibrosis.

Index	Training cohort		*P* Value	Validation cohort		*P* Value
	Estimate	95%CI		Estimate	95%CI	
NRI						
For 1-year CSS	0.42	0.27–0.56		0.26	0.17–0.46	
For 3-year CSS	0.61	0.50–0.77		0.52	0.22–0.76	
For 5-year CSS	0.67	0.49–0.80		0.72	0.44–0.92	
IDI						
For 1-year CSS	0.16	0.12–0.19	<0.001	0.17	0.11–0.22	<0.001
For 3-year CSS	0.20	0.17–0.23	<0.001	0.26	0.21–0.32	<0.001
For 5-year CSS	0.22	0.19–0.28	<0.001	0.30	0.23–0.36	<0.001

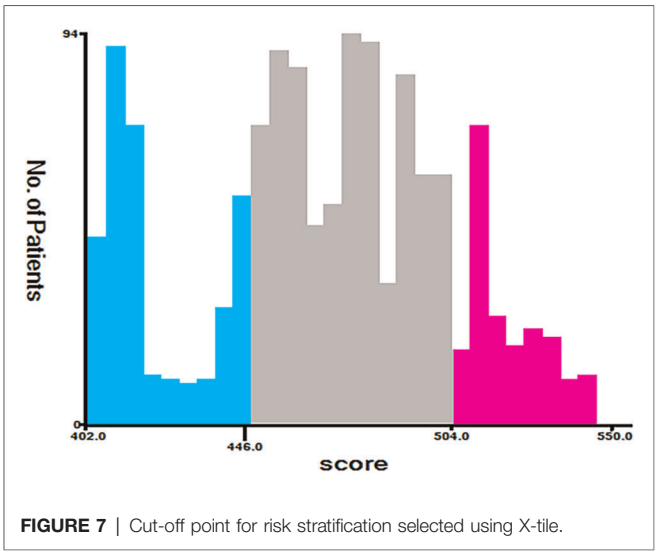

FIGURE 7 | Cut-off point for risk stratification selected using X-tile.

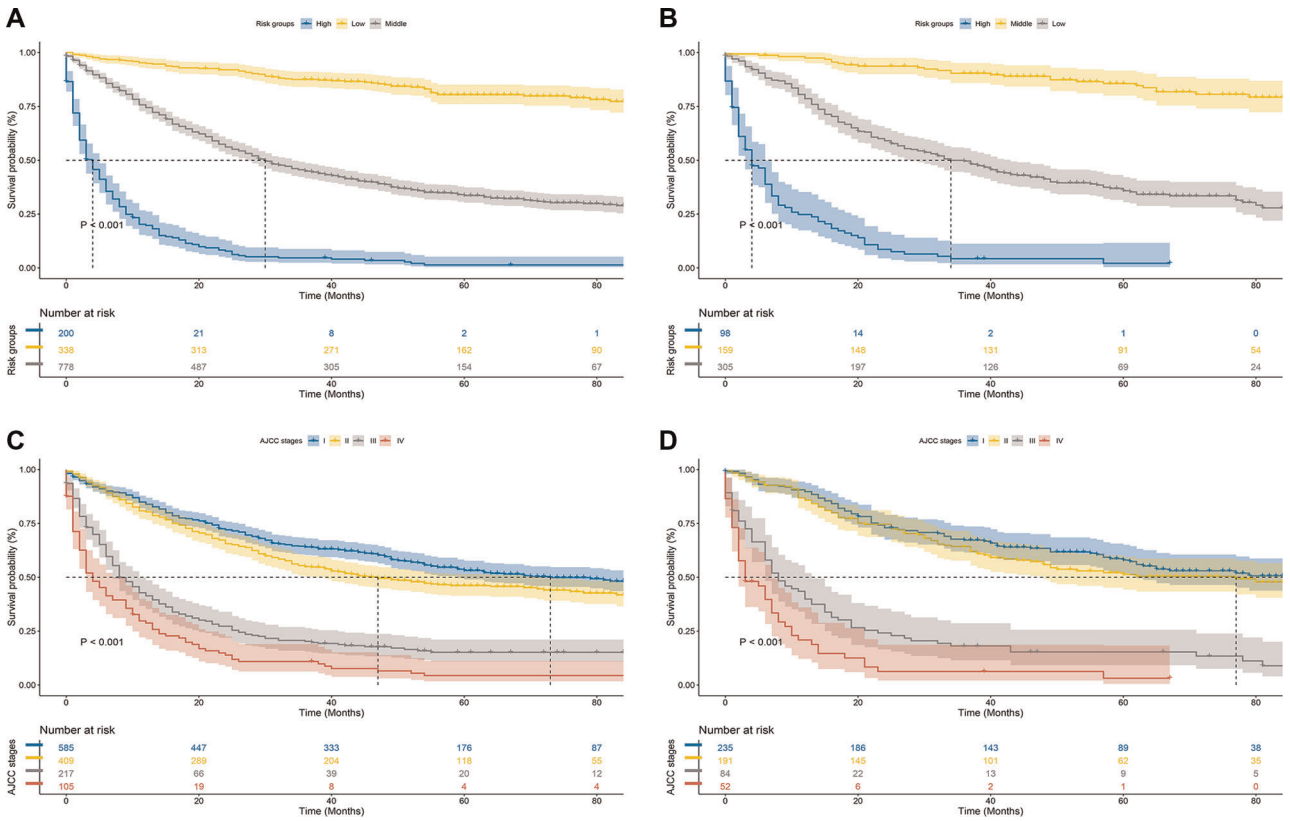

FIGURE 8 | Kaplan–Meier CSS curves of hepatocellular carcinoma patients with severe liver fibrosis based on different criteria. (**A,B**) Kaplan–Meier CSS curves of training and validation cohorts based on the new risk stratification system; (**C,D**) Kaplan–Meier CSS curves of training and validation cohorts based on AJCC staging criteria.

Consequently, some surgeons will choose AFP models to select HCC patients who may not match Milan transplantation criteria (24). In addition, researchers are working on constructing a predictive model including AFP for HCC that involves Child B liver function. CSS is noticeably shorter in AFP-positive patients than in AFP-negative patients, which reveals that AFP exhibits a substantial predictive value in predicting long-term CSS in HCC patients with severe liver fibrosis (25, 26).

Currently, HCC is treated with chemotherapy, local therapy, mass resection, and liver transplantation. Nevertheless, there is no universally accepted treatment for HCC with severe liver fibrosis. HCC patients with severe hepatic fibrosis and those with slight liver fibrosis had diverse prognoses in previous decades (27, 28). Furthermore, it is widely considered that surgery may worsen the prognosis of HCC patients with severe liver fibrosis. Several guidelines have recommended chemotherapy, combined with local therapy, as the first-line treatment for HCC patients with severe liver fibrosis (29, 30). However, with the implementation and advancement of minimally invasive techniques in clinical practice, the rates of postoperative liver failure, mortality, and infection have decreased significantly (31, 32). Thus, surgery may provide better long-term benefits than local therapy based on acceptable short-term postoperative mortality and infection rates. According to existing studies, the five-year postoperative survival rate for HCC patients with severe liver fibrosis is up to 35% (32–34). Several of the most influential hepatobiliary institutions have argued that HCC in the presence of significant liver fibrosis is not an absolute contraindication to surgery and that patients with grade B or even C liver cancer can benefit from surgery (35, 36).

Despite the promising application of the nomogram in predicting CSS in HCC with severe liver fibrosis, this study had several limitations. First, the data lacked information on patient etiology, for instance, hepatitis B or C virus infection and alcoholic liver disease, which might affect tumor characteristics. Moreover, data on hematological indicators and surgical margins were not recorded. Finally, our model lacked a multicenter clinical sample for further validation to provide more convincing evidence.

CONCLUSION

In conclusion, a practical and reliable nomogram for predicting CSS for HCC patients with severe liver fibrosis was constructed based on the significant risk factors identified in the analysis, which could effectively solve the survival paradox caused by the AJCC staging system and might help physicians make appropriate clinical decisions.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The SEER database was made publicly available and the private data of all patients were eliminated from the database. Therefore, informed consent and institutional review board approval were not required.

AUTHOR CONTRIBUTIONS

Conceptualization was done by DY, YS, and FZ, data curation was performed by CC and KZ, formal analysis was conducted by DY, XX, and YS, writing of the original draft was done by DY, YS, and FZ, and the work of writing the review and editing was taken up by YD. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.920589/full#supplementary-material.

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Prognostic Nomograms Combined Adjuvant Lenvatinib for Hepatitis B Virus–related Hepatocellular Carcinoma With Microvascular Invasion After Radical Resection

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Background and Aim: Microvascular invasion (MVI) has been established as one of the most important contributors to the prognosis of primary hepatocellular carcinoma (HCC). The objective of this study was to investigate the potential effect of postoperative adjuvant therapy with lenvatinib on the long-term prognosis after radical resection in hepatitis B virus (HBV)-related HCC patients with MVI, as well as to predict the long-term survival based on nomograms.

Methods: Data from 293 HBV-related hepatocellular carcinoma patients with histologically confirmed MVI who underwent R0 resection at Eastern Hepatobiliary Surgery Hospital (EHBH) was retrospectively analyzed. 57 patients received postoperative adjuvant therapy with lenvatinib, while 236 patients did not. The survival outcome of patients who received postoperative adjuvant lenvatinib versus those who did not was analyzed.

Results: The 1-year, 2-year recurrence rates and survival rates of the lenvatinib group were improved compared to the non-lenvatinib group (15.9%, 43.2% vs 40.1%, 57.2%, P=0.002; 85.8%, 71.2% vs 69.6%, 53.3%, P=0.009, respectively). Similar findings were also observed after Propensity Score Matching (PSM) compared to non-PSM analyses The 1-year, 2-year recurrence rates and survival rates were more favorable for the lenvatinib group compared to the non-lenvatinib group (15.9%, 43.2% vs 42.1%, 57.4%, P=0.028; 85.8%, 71.2% vs 70.0%, 53.4%, P=0.024, respectively). As shown by univariate and multivariate analyses, absence of adjuvant lenvatinib treatment was identified as an independent risk factor for recurrence and survival. The established nomograms displayed good performance for the prediction of recurrence and survival, with a C-index of 0.658 and 0.682 respectively.

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Conclusions: Postoperative adjuvant therapy with lenvatinib was associated with improved long-term prognosis after R0 Resection in HBV-related HCC patients with MVI, which could be accurately predicted from nomograms.

Keywords: hepatocellular carcinoma, lenvatinib, propensity score matching (PSM), nomogram, microvascular invasion

INTRODUCTION

Primary hepatocellular carcinoma (HCC) is the sixth most commonly occurring malignancy and the third leading cause of cancer-related mortality worldwide (1). Radical treatment for early and intermediate stages of HCC primarily includes hepatectomy and liver transplantation. As a result of the limited availability and exorbitant cost of liver transplantation, hepatectomy is considered as the first choice for the radical cure of HCC (2). However, the 5-year postoperative recurrence rate of HCC remains as high as 70%-80% (3, 4) The presence of microvascular invasion (MVI) indicates a more aggressive HCC, and patients in this setting may display earlier recurrence and distant metastasis. Therefore, MVI is currently considered as one of the most critical predictors of HCC recurrence (5, 6). Previous studies have shown a prevalence of MVI ranging from 15.0% to 57.1% in samples obtained from hepatectomy or liver transplantation (5).

As a novel molecular targeted agent, lenvatinib is an oral multi-kinase inhibitor that is predominantly active against VEGFR 1-3, FGFR 1-4, PDGF receptor-alpha, RET and KIT (7). In the REFLECT study, non-inferiority in overall survival rate and significant improvement in progression-free survival, time to progression, time to progression, objective response rate, and safety were demonstrated for lenvatinib compared to sorafenib in patients with advanced unresectable HCC (7). As shown by the subgroup analysis, the overall survival was substantially longer in patients with HBV-related HCC who received lenvatinib compared to those who were given sorafenib. Currently, lenvatinib is recommended as a first-line treatment for unresectable HCC in NCCN, ECMO, AASLD, EASL and Chinese clinical guidelines for the management of HCC (8–12).

Postoperative adjuvant treatments, including TACE, sorafenib and Huaier Granule, improved the long-term prognosis after radical hepatectomy in HCC patients with MVI (13–15). However, whether the postoperative adjuvant treatment with lenvatinib as anti-recurrence therapy improves the prognosis of Hepatitis B Virus–related HCC with MVI after Radical Resection has not been described.

Therefore, 57 patients who received postoperative adjuvant therapy with lenvatinib and 236 patients who did not were included in this study, with the purpose of analyzing the long-term prognosis of these two groups and establishing nomograms to predict the long-term survival of the patients.

Patient Selection

The study enrolled 293 HBV-related HCC patients with MVI who underwent radical hepatectomy at Eastern Hepatobiliary Surgery Hospital (The Third Affiliated Hospital of People's Liberation Army Naval Medical University) from June 1, 2019 to June 1, 2021, including 57 patients who received postoperative adjuvant therapy with lenvatinib and 236 patients who did not. This study was approved by the Institutional Ethics Committee of the hospital and each patient signed the informed consent to collect his/her data for the purpose of the study. The inclusion criteria included: 1. Pathological diagnosis of HCC; 2. Child - Pugh A or B7 (16); 3. Had not received any anti-tumor treatment before surgery; 4. R0 resection with pathological diagnosis of M1 or M2; 5. Aged 18-70 years; and 6. ECOG score of 0 or 1. The exclusion criteria included: 1. R0 resection with pathological diagnosis of M0;2. Child-Pugh beyond B7, presence of CSPH or refractory ascites; 3.Had received preoperative anti-tumor treatment; 4. Medical histories of other tumors; 5. AFP can't decreased to the normal level as re-determined in one month after surgery; 6.Elective surgery due to tumor rupture; and 7. incomplete clinical data.

Retrospective variables included age, sex, hepatitis B virus-deoxyribonucleic acid(HBV-DNA), total bilirubin(TBIL), albumin(ALB), alanine aminotransferase(ALT), platelet count(PLT), prothrombin time(PT), neutrophil-to-lymphocyte ratio(NLR), alpha fetoprotein (AFP), blood transfusion, and resection margin. Tumor pathological data included maximum tumor diameter, tumor number, MVI, tumor capsule, tumor differentiation and liver cirrhosis classification. MVI was defined as the presence of cancer cell nests in portal and hepatic veins lined with endothelial cells, as well as in tumor capsular vessels (17); M1 (1–5 sites of MVI occurring in the tumor-adjacent liver tissue ≤ 1 cm away from the main tumor), M2 (> 5 MVI sites, or any MVI existing in the distant liver tissue > 1 cm away from the main tumor) (17). A wide or narrow resection margin was defined as the shortest distance ≥1 cm or <1 cm from the tumor edge to the LR plane, which was consistent to the definition described elsewhere (18–20). Early recurrence was defined as recurrence within 1 year after surgery (21, 22).

Usage of Lenvatinib

Patients in the lenvatinib group were given oral lenvatinib (Eisai, Japan) 12 mg/d (B.W. ≥ 60 kg) or 8 mg/day (B.W. < 60 kg) on a 28-day cycle, until HCC recurrence, serious adverse events (SAE) or spontaneous withdrawal. Interruption or dose reduction was allowed to alleviate toxicities related to lenvatinib

(with the dose reduced to 8 mg and 4 mg per day or 4 mg every other day). Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 4.0.

Postoperative Follow-Up

All the patients received prophylactic TACE for about a month after surgery (23). Testing of AFP as a tumor marker in peripheral blood, ultrasonography, and contrast-enhanced CT or magnetic resonance imaging (MRI) of the abdomen were completed in follow-up visits which were performed every 2 months during the first 6 month and every half year thereafter. Study endpoints included overall survival (OS) and time to recurrence (TTR). OS was determined based on the duration from the date of liver resection to the date of death or the last follow-up. In contrast, TTR was calculated from the date of liver resection to that of the first HCC recurrence or the last follow-up.

Statistical Analysis

Statistical analysis was conducted using R software version 4.0.0, (http://www.R-project.org). Continuous variables of normal distribution were expressed as mean ± standard deviation. Categorical variables were denoted with number (n) or proportion (%). Continuous variables were compared using independent samples t-test if applicable; otherwise, Mann–Whitney U test was employed. Categorical variables were compared using the Chi-square test or Fisher's exact test if appropriate. A 1:1 propensity score matching (PSM) was performed to adjust for confounding factors between two groups. The binary logistic regression with selected variables was used to produce continuous propensity scores from 0 to 1. The nearest-neighbor match between with and without adjuvant lenvatinib patients was performed to select patients for subsequent analyses and the pairs on the propensity-score logit were then matched to within a range of 0.2 of standard deviation. OS and TTR were calculated by the Kaplan–Meier method generated by the log-rank test. Independent risk factors for OS and TTR were identified based on univariate and multivariate Cox regression analyses. As for variables with $P<0.05$ in univariate analysis, analyses were implemented using a multivariate Cox regression model with a positive stepwise variable selection method. The statistical significance level was set at $P<0.05$ for all analyses.

RESULTS

Demographic Characteristics and Clinical Data

Among 896 HCC patients who underwent radical hepatic resection in our hospital, 603 patients were excluded. Two hundred and ninety-three (293) patients were enrolled (**Figure S1**), including 57 patients who received postoperative adjuvant treatment with lenvatinib and 236 patients who did not.

TABLE 1 | Basal clinicopathological characteristics of 293 HCC patients with Microvascular Invasion with and without adjuvant Lenvatinib.

Variable	Before PSM			After PSM		
	No Lenvatinib (n = 236)	Lenvatinib (n = 57)	*P*	No Lenvatinib (n = 57)	Lenvatinib (n = 57)	*P*
Age	52 (21-69)	53 (20-70)	0.265	52 (21-69)	53 (20-70)	0.135
Gender			0.073			0.178
Female	213 (90.3)	46 (80.7)		52 (91.2)	46 (80.7)	
Male	23 (9.75)	11 (19.3)		5 (8.77)	11 (19.3)	
HBV-DNA, IU/mL			**0.004**			1.000
≤2000	105 (44.5)	38 (66.7)		37 (64.9)	38 (66.7)	
>2000	131 (55.5)	19 (33.3)		20 (35.1)	19 (33.3)	
TBIL, μmol/L			0.399			1.000
≤17	162 (68.6)	43 (75.4)		44 (77.2)	43 (75.4)	
>17	74 (31.4)	14 (24.6)		13 (22.8)	14 (24.6)	
ALB, g/L			0.258			0.679
≤35	8 (3.39)	4 (7.02)		2 (3.51)	4 (7.02)	
>35	228 (96.6)	53 (93.0)		55 (96.5)	53 (93.0)	
ALT, U/L			0.195			0.702
≤44	124 (52.5)	36 (63.2)		33 (57.9)	36 (63.2)	
>44	112 (47.5)	21 (36.8)		24 (42.1)	21 (36.8)	
PLT, $*10^9$/ml			1.000			0.178
≤100	44 (18.6)	11 (19.3)		5 (8.77)	11 (19.3)	
>100	192 (81.4)	46 (80.7)		52 (91.2)	46 (80.7)	
PT, S			**0.032**			1.000
≤13	183 (77.5)	52 (91.2)		53 (93.0)	52 (91.2)	
>13	53 (22.5)	5 (8.77)		4 (7.02)	5 (8.77)	
NLR			0.614			0.064
≤2.4	159 (67.4)	41 (71.9)		29 (50.9)	37 (64.9)	
>2.4	77 (32.6)	16 (28.1)		28 (49.1)	20 (35.1)	
AFP, ng/mL			**0.007**			1.000

(Continued)

TABLE 1 | Continued

Variable	Before PSM			After PSM		
	No Lenvatinib (n = 236)	Lenvatinib (n = 57)	*P*	No Lenvatinib (n = 57)	Lenvatinib (n = 57)	*P*
≤400	88 (37.3)	33 (57.9)		33 (57.9)	33 (57.9)	
>400	148 (62.7)	24 (42.1)		24 (42.1)	24 (42.1)	
Transfusion			0.378			0.164
No	157 (66.5)	42 (73.7)		34 (59.6)	42 (73.7)	
Yes	79 (33.5)	15 (26.3)		23 (40.4)	15 (26.3)	
Tumor diameter, cm			0.515			1.000
≤5	54 (22.9)	16 (28.1)		17 (29.8)	16 (28.1)	
>5	182 (77.1)	41 (71.9)		40 (70.2)	41 (71.9)	
Tumor number			0.389			0.823
1	200 (84.7)	45 (78.9)		43 (75.4)	45 (78.9)	
≥2	36 (15.3)	12 (21.1)		14 (24.6)	12 (21.1)	
Microvascular invasion			**0.049**			1.000
M1	168 (71.1)	31 (54.3)		33 (57.8)	31 (54.3)	
M2	68 (28.9)	26 (45.7)		24 (42.2)	26 (45.7)	
Tumor capsule			0.770			1.000
Complete	129 (54.7)	33 (57.9)		32 (56.1)	33 (57.9)	
Incomplete	107 (45.3)	24 (42.1)		25 (43.9)	24 (42.1)	
Margin			0.283			0.430
Narrow	91 (38.6)	17 (29.8)		22 (38.6)	17 (29.8)	
Wide	145 (61.4)	40 (70.2)		35 (61.4)	40 (70.2)	
Edmondson-Steiner grade			0.096			1.000
I-II	10 (4.24)	6 (10.5)		5 (8.77)	6 (10.5)	
III-VI	226 (95.8)	51 (89.5)		52 (91.2)	51 (89.5)	
Cirrhosis			1.000			0.254
No	85 (36.0)	20 (35.1)		27 (47.4)	20 (35.1)	
Yes	151 (64.0)	37 (64.9)		30 (52.6)	37 (64.9)	

Bold values indicate statistical significance (P < 0.05).

HCC, Hepatocellular Carcinoma; PSM, propensity score matching. HBV-DNA, hepatitis B virus-deoxyribonucleic acid; TBIL, total bilirubin; ALB, albumin; ALT, Alanine aminotransferase; PT, Prothrombin time; PLT, platelet; NLR, neutrophil-to-lymphocyte ratio; AFP, alpha fetoprotein.

Comparison of the clinical data of the two groups is shown in **Table 1**. Statistical differences were observed in HBV-DNA, PT, AFP and MVI. In order to eliminate potential bias induced by differences in baselines characteristics, PSM was implemented for the two groups. The lenvatinib and non-lenvatinib groups both included 57 patients after PSM (**Table 1**).

Adverse Events of Lenvatinib

In the lenvatinib group, all the patients tolerated the oral treatment with lenvatinib for at least three cycles, although 18 patients had their dose reduced due to adverse reactions of CTCAE grade 2, and 5 patients discontinued lenvatinib treatment after the dose reduction. The occurrence of adverse reactions in the lenvatinib group is presented in **Table 2**. The overall incidence of adverse reactions was 87.7% (50/57). Hypertension was identified to be the most common adverse reaction, and no fatal adverse event was reported. The most severe adverse events were 5 events of CTCAE grade 3.

Survival Analysis

The median follow-up was 22.6 months for the lenvatinib group, and 22.4 months for the non-lenvatinib group. Before PSM, both the TTR and OS in the lenvatinib group were significantly improved compared to those in the non-lenvatinib group

TABLE 2 | Adverse events in treatment of adjuvant Lenvatinib after radical resection and their corresponding common terminology criteria for adverse events (CTCAE) grade.

Adverse events	Adjuvant Lenvatinib (n = 57)			
	All	Grade 1	Grade 2	Grade 3
Hypertension	20	10	7	3
PPES	13	7	5	1
Diarrhoea	19	9	8	2
Fatigue	15	9	6	0
Decreased appetite	16	7	9	0
Hypothyroidism	6	4	2	0
DILI	17	10	6	1
Others	10	7	3	0

PPES, palmar-plantar erythrodysesthesia syndrome; DILI, drug-induced liver injury.

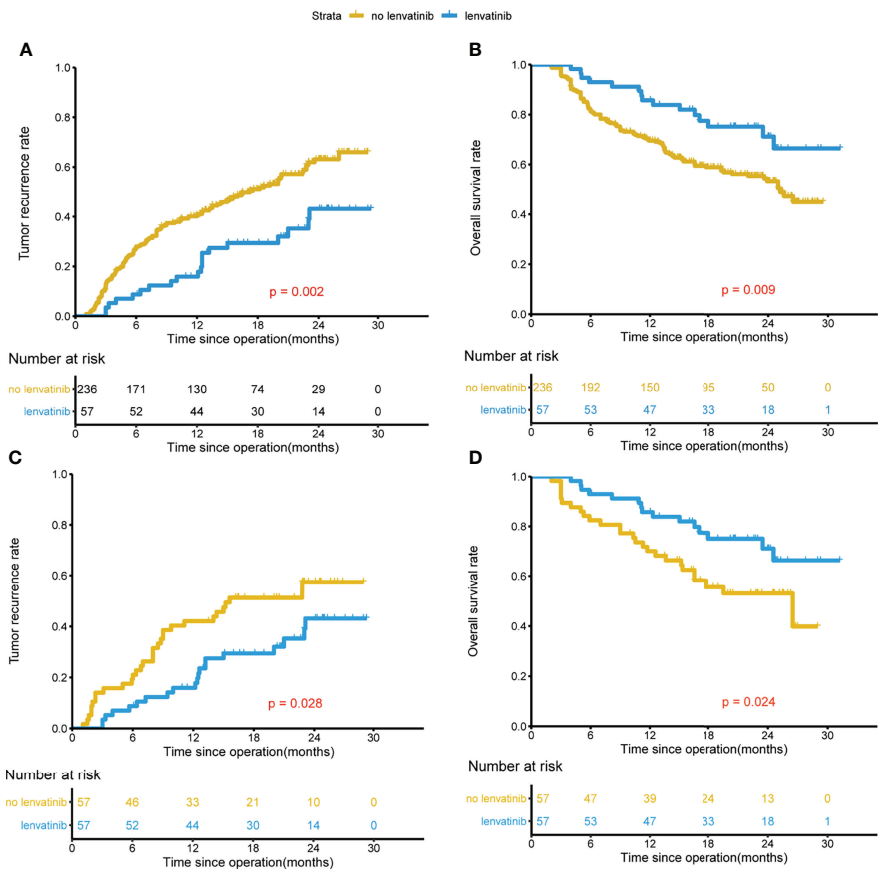

FIGURE 1 | Kaplan-Meier analysis for predicting survival in HCC patients with MVI after radical resection. Before PSM, TTR and OS for patients with and without adjuvant Lenvatinib **(A, B)**. After PSM, TTR and OS for patients with and without adjuvant Lenvatinib **(C, D)**.

(1-year and 2-year recurrence rates were 15.9%, 43.2% and 40.1%, 57.2% respectively, P=0.002; 1-year and 2-year survival rates were 85.8%, 71.2% and 69.6%, 53.6% respectively, P=0.009) (**Figures 1A, B**). After PSM, similar results were found compared to those before PSM (1-year and 2-year recurrence rates were 15.9%, 43.2% and 42.1%, 57.6% respectively, P=0.028; 1-year and 2-year survival rates were 85.8%, 71.2% and 70.0%, 53.4% respectively, P=0.024) (**Figures 1C, D**). In the group with MVI beings M1, lenvatinib group had better TTR and OS than non-lenvatinib group (**Figures 2A, B**), Similar results were noted in the group with MVI being M2 (**Figures 2C, D**).

Among the 57 patients in the lenvatinib group, 20 (35.1%) patients relapsed, including 9 patients with early recurrence and 11 patients with late recurrence. In the non-lenvatinib group, 124/236 (52.5%) patients relapsed, including 94 patients with early recurrence and 30 patients with late recurrence. Statistical differences were observed between the two groups in the number of patients with recurrence and the proportion of early recurrences (P=0.026, P=0.010). Among the 124 patients in the non-lenvatinib group, 104 patients had intrahepatic recurrence, 8 patients had extrahepatic recurrence, and 12 patients had both intrahepatic and extrahepatic recurrence. Among the 20 patients with recurrence in the lenvatinib group, 16 patients had intrahepatic recurrence, 2 patients had extrahepatic recurrence, and 2 patient had both intrahepatic and extrahepatic recurrence. There was no statistical difference in the recurrence pattern between the two groups (P=0.785) (**Table 3**). After PSM, the incidence of early recurrence in the lenvatinib group were significantly lower compared to those in the non-lenvatinib group(P=0.038).

Risk Factors for Poor TTR and OS

Before PSM, univariate analysis and multivariate analysis showed AFP>400ng/ml (P=0.025), multiple tumors(P=0.006), MVI being M2 (P<0.001), narrow resection margin (P<0.001) and absence of adjuvant lenvatinib (P=0.001) were identified as independent risk factors for postoperative recurrence. HBV-DNA>2000 IU/mL (P=0.023), AFP>400 ng/mL (P=0.028), multiple tumors (P=0.002), MVI being M2 (P<0.001), narrow resection margin (P<0.001) and postoperative adjuvant lenvatinib (P=0.002) were identified as independent risk factors for postoperative survival (**Tables 4**, **5**). After PSM, NLR>2.4 (P=0.022), MVI being M2 (P=0.019), narrow resection margin (P=0.021)and absence of adjuvant

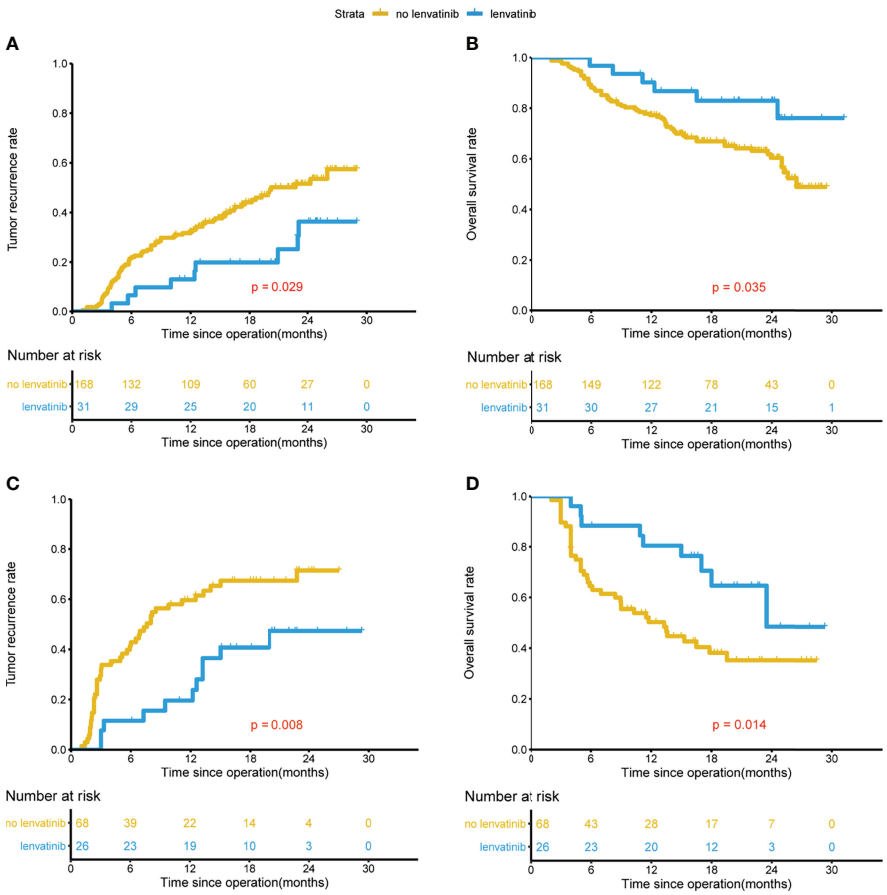

FIGURE 2 | Kaplan-Meier analysis for predicting survival in HCC patients with MVI beings M1 and M2 after radical resection. MVI beings M1, TTR and OS for patients with and without adjuvant Lenvatinib **(A, B)**. MVI beings M2, TTR and OS for patients with and without adjuvant Lenvatinib **(C, D)**.

lenvatinib (0.039) were identified as independent risk factors for postoperative recurrence; and NLR>2.4 (P=0.010), MVI being M2 (P=0.017), narrow resection margin (P=0.024)and absence of adjuvant lenvatinib (0.048) were found to be independent risk factors for postoperative long-term survival (**Tables 6**, **7**).

Prognostic Nomograms for TTR and OS Before PSM

Based on the independent risk factors associated with recurrence and survival identified before PSM, nomograms were established (**Figures 3A, B**). The C-index were 0.658 and 0.682 for TTR and OS prediction. As shown in the calibration curves for 1-year, 2-

TABLE 3 | Patterns of recurrence in HCC with Microvascular Invasion with and without adjuvant Lenvatinib.

Parameters	Before PSM (n, %)			After PSM (n, %)		
	No Lenvatinib (n = 236)	Lenvatinib (n = 57)	*P*	No Lenvatinib (n = 57)	Lenvatinib (n = 57)	*P*
No. of recurrent cases	124 (52.5)	20 (35.1)	**0.026**	31 (54.4)	20 (35.1)	0.059
Time to recurrence, months*			**0.010**			**0.038**
≤12	94 (75.8)	9 (45.0)		24 (77.4)	9 (47.3)	
>12	30 (24.2)	11 (55.0)		7 (22.6)	11 (52.7)	
Type of recurrence**			0.785			1.000
Intrahepatic	104 (84.0)	16 (80)		24 (77.4)	16 (80)	
Extrahepatic	8 (6.4)	2 (10)		4 (12.9)	2 (10)	
Intra- plus extrahepatic	12 (9.6)	2 (10)		3 (10.7)	2 (10)	

Bold values indicate statistical significance (P < 0.05). HCC, Hepatocellular Carcinoma; PSM, propensity score matching.

TABLE 4 | Univariate Cox-regression analysis for predicting TTR and OS in 293 HCC patients with Microvascular Invasion with and without adjuvant Lenvatinib before PSM.

Variable	Univariate Analysis (TTR)			Univariate Analysis (OS)		
	HR	95%CI	*P*	HR	95%CI	*P*
Age, years	0.99	0.97-1.00	0.117	0.99	0.97-1.00	0.108
Gender, Male vs. Female	0.85	0.50-1.45	0.545	0.79	0.43-1.43	0.435
HBV-DNA, IU/mL >2000 vs. ≤2000	1.68	1.21-2.35	**0.002**	1.89	1.30-2.73	**0.001**
TBIL, μmol/L >2000 vs. ≤2000	0.97	0.68-1.39	0.869	0.88	0.59-1.31	0.518
ALB, g/L >35 vs. ≤35	1.75	0.65-4.74	0.268	1.38	0.51-3.74	0.528
ALT, U/L >44 vs. ≤44	0.89	0.64-1.23	0.472	0.80	0.56-1.16	0.237
PLT, $\times10^9$/L >100 vs. ≤100	0.92	0.61-1.39	0.687	0.92	0.59-1.43	0.703
PT, seconds >13 vs. ≤13	0.91	0.59-1.38	0.646	1.08	0.69-1.69	0.733
NLR >2.4 vs. ≤2.4	1.66	1.18-2.32	**0.003**	1.69	1.17-2.45	**0.005**
AFP, ng/mL >400 vs. ≤400	1.63	1.16-2.29	**0.005**	1.74	1.19-2.55	**0.005**
Transfusion Yes vs. no	1.16	0.82-1.63	0.399	1.03	0.71-1.51	0.870
Tumor diameter, cm >5 vs. ≤5	1.52	1.00-2.31	0.051	1.54	0.97-2.46	0.067
Tumor number Multiple vs. Single	1.63	1.07-2.46	**0.021**	1.90	1.23-2.94	**0.004**
Microvascular invasion M2 vs. M1	1.83	1.31-2.56	**<0.001**	2.00	1.38-2.88	**<0.001**
Tumor capsule Incomplete vs. Complete	0.79	0.56-1.10	0.161	0.79	0.55-1.14	0.203
Margin Wide vs. Narrow	0.54	0.39-0.76	**<0.001**	0.52	0.36-0.75	**<0.001**
Edmondson-Steiner grade III-VI vs. I-II	0.93	0.49-1.77	0.826	1.68	0.68-4.11	0.258
Cirrhosis Yes vs. No	1.31	0.93-1.86	0.127	1.28	0.87-1.88	0.205
Lenvatinib Yes vs. No	0.52	0.32-0.83	**0.006**	0.49	0.29-0.85	**0.011**

Bold values indicate statistical significance (P < 0.05). HCC, Hepatocellular Carcinoma; PSM, propensity score matching; OS, overall survival; TTR, time to recurrence; HBV-DNA, hepatitis B virus-deoxyribonucleic acid; TBIL, total bilirubin; ALB, albumin; ALT, Alanine aminotransferase; PT, Prothrombin time; PLT, platelet; NLR, neutrophil-to-lymphocyte ratio; AFP, alpha fetoprotein.

TABLE 5 | Multivariate Cox-regression analysis for predicting TTR and OS in 293 HCC patients with Microvascular Invasion with and without adjuvant Lenvatinib before PSM.

Variable	Multivariable Analysis (TTR)			Multivariable Analysis (OS)		
	HR	95%CI	P	HR	95%CI	P
HBV-DNA, IU/mL >2000 vs. ≤2000	–	–	–	1.56	1.06-2.29	**0.023**
AFP, ng/mL >400 vs. ≤400	1.50	1.05-2.15	**0.025**	1.56	1.05-2.33	**0.028**
Tumor number Multiple vs. Single	1.83	1.19-2.81	**0.006**	2.07	1.31-3.25	**0.002**
Microvascular invasion M2 vs. M1	2.22	1.54-3.22	**<0.001**	2.37	1.59-3.55	**<0.001**
Margin Wide vs. Narrow	0.50	0.35-0.71	**<0.001**	0.47	0.32-0.69	**<0.001**
Lenvatinib Yes vs. No	0.44	0.27-0.72	**0.001**	0.42	0.24-0.73	**0.002**

Bold values indicate statistical significance (P < 0.05). OS, overall survival; TTR, time to recurrence; HCC, Hepatocellular Carcinoma; PSM, propensity score matching. HBV-DNA, hepatitis B virus-deoxyribonucleic acid; AFP, alpha fetoprotein.

TABLE 6 | Univariate Cox-regression analysis for predicting TTR and OS in 114 HCC patients with Microvascular Invasion with and without adjuvant Lenvatinib after PSM.

Variable	Univariate Analysis (TTR)			Univariate Analysis (OS)		
	HR	95%CI	*P*	HR	95%CI	*P*
Age, years	0.99	0.97-1.01	0.312	0.99	0.96-1.01	0.291
Gender, Male vs. Female	0.64	0.26-1.62	0.350	0.65	0.23-1.83	0.415
HBV-DNA, IU/mL Negative vs. Positive	1.46	0.83-2.57	0.187	1.42	0.76-2.68	0.273
TBIL, μmol/L >2000 vs. ≤2000	1.32	0.70-2.48	0.388	1.21	0.59-2.47	0.605
ALB, g/L >35 vs. ≤35	0.89	0.28-2.87	0.848	0.71	0.22-2.31	0.573
ALT, U/L >44 vs. ≤44	0.77	0.43-1.37	0.380	0.64	0.33-1.24	0.187
PLT, $\times10^9$/L >100 vs. ≤100	0.85	0.40-1.81	0.674	0.71	0.33-1.55	0.396
PT, seconds >13 vs. ≤13	1.81	0.77-4.26	0.171	2.09	0.88-4.97	0.096
NLR >2.4 vs. ≤2.4	2.62	1.50-4.59	**0.001**	2.78	1.48-5.24	**0.001**
AFP, ng/mL >400 vs. ≤400	2.10	1.21-3.65	**0.009**	1.73	0.93-3.22	0.081
Transfusion Yes vs. no	1.64	0.94-2.86	0.079	1.45	0.78-2.70	0.242
Tumor diameter, cm >5 vs. ≤5	1.04	0.56-1.93	0.904	0.87	0.45-1.69	0.679
Tumor number Multiple vs. Single	1.41	0.75-2.65	0.288	1.54	0.77-3.08	0.222
Microvascular invasion M2 vs. M1	2.06	1.18-3.59	**0.011**	2.07	1.11-3.86	**0.022**
Tumor capsule Incomplete vs. Complete	0.60	0.33-1.07	0.084	0.69	0.36-1.30	0.246
Margin Wide vs. Narrow	0.55	0.31-0.96	**0.035**	0.51	0.27-0.94	**0.031**
Edmondson-Steiner grade III-VI vs. I-II	0.61	0.28-1.29	0.193	0.91	0.35-2.34	0.846
Cirrhosis Yes vs. No	1.60	0.89-2.87	0.114	1.43	0.75-2.74	0.273
Lenvatinib Yes vs. No	0.54	0.31-0.94	**0.030**	0.49	0.26-0.92	**0.026**

Bold values indicate statistical significance (P < 0.05). HCC, Hepatocellular Carcinoma; PSM, propensity score matching; OS, overall survival; TTR, time to recurrence; HBV-DNA, hepatitis B virus-deoxyribonucleic acid; TBIL, total bilirubin; ALB, albumin; ALT, Alanine aminotransferase; PT, Prothrombin time; PLT, platelet; NLR, neutrophil-to-lymphocyte ratio; AFP, alpha fetoprotein.

TABLE 7 | Multivariate Cox-regression analysis for predicting TTR and OS in 114 HCC patients with Microvascular Invasion with and without adjuvant Lenvatinib after PSM.

Variable	Multivariable Analysis (TTR)			Multivariable Analysis (OS)		
	HR	95%CI	P	HR	95%CI	P
NLR >2.4 vs. ≤2.4	1.98	1.10-3.57	**0.022**	2.34	1.23-4.46	**0.010**
Microvascular invasion M2 vs. M1	2.00	1.12-3.56	**0.019**	2.18	1.15-4.13	**0.017**
Margin Wide vs. Narrow	0.51	0.28-0.90	**0.021**	0.49	0.26-0.91	**0.024**
Lenvatinib Yes vs. No	0.55	0.31-0.97	**0.039**	0.52	0.28-0.99	**0.048**

Bold values indicate statistical significance (P < 0.05). OS, overall survival; TTR, time to recurrence; HCC, Hepatocellular Carcinoma; PSM, propensity score matching. NLR, neutrophil-to-lymphocyte ratio.

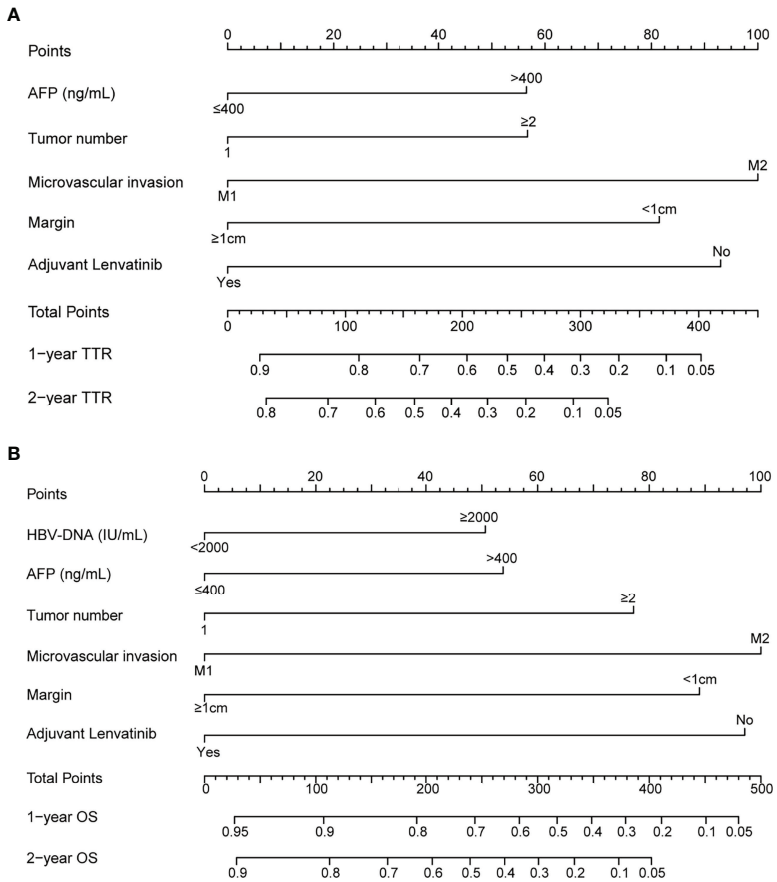

FIGURE 3 | Nomogram for survival of HCC patients with MVI after radical resection. adjuvant Lenvatinib-related nomograms for TTR **(A)** and OS **(B)**.

year recurrence and survival rates, nomogram predictions and actual observations appeared to be highly comparable (**Figure 4**).

DISCUSSION

HCC is one of the most commonly diagnosed malignancies worldwide (24). Over the past several decades, treatment of HCC has evolved to a great extent. Surgical resection has been recognized as the first-line treatment for HCC in its early and intermediate stages. Unfortunately, the recurrence rate remains high after resection and the long-term survival is found to be very low, especially in patients with vascular invasion (25, 26). How to delay the recurrence of HCC patients remains to be a challenge in the treatment of HCC.

This study aimed to investigate the safety and prognosis of postoperative adjuvant lenvatinib anti-recurrence therapy in HBV-related HCC patients with MVI to guide rational clinical decision making. In this study, adjuvant lenvatinib after radical hepatectomy reduced the early recurrence rate and prolonged the OS. Similar results were obtained after bias due to baseline differences was eliminated by PSM. Adverse events of adjuvant lenvatinib treatment were generally manageable. The present study is the first to describe the use of lenvatinib as an adjuvant therapy to reduce the risk of postoperative recurrence and improve long-term survival outcomes in HBV-related HCC patients with MVI.

MVI is acknowledged as an expression of aggressive biological behavior of the tumor and is currently one of the most critical factors predicting HCC recurrence (5, 27, 28).The presence of MVI is a key determinant of recurrence and prognosis after hepatectomy for early-stage HCC. Improving the prognosis of MVI-positive HCC represents a major challenge for liver oncology surgery. As there is no effective way to diagnose MVI before surgery, adjuvant therapy, such as postoperative adjuvant TACE, and radiotherapy, has been used after hepatectomy to improve the prognosis of this group of patients (14, 23, 29, 30). Before the introduction of lenvatinib, sorafenib was the first and only molecule-targeted drug approved for HCC treatment, and the effects of sorafenib on the prevention of HCC recurrence after liver resection have been evaluated (13, 31). Huang et al. demonstrated both improved tumor-free survival and OS with postoperative adjuvant sorafenib in MVI-positive patients (31). In another study described by Zhang et al.,

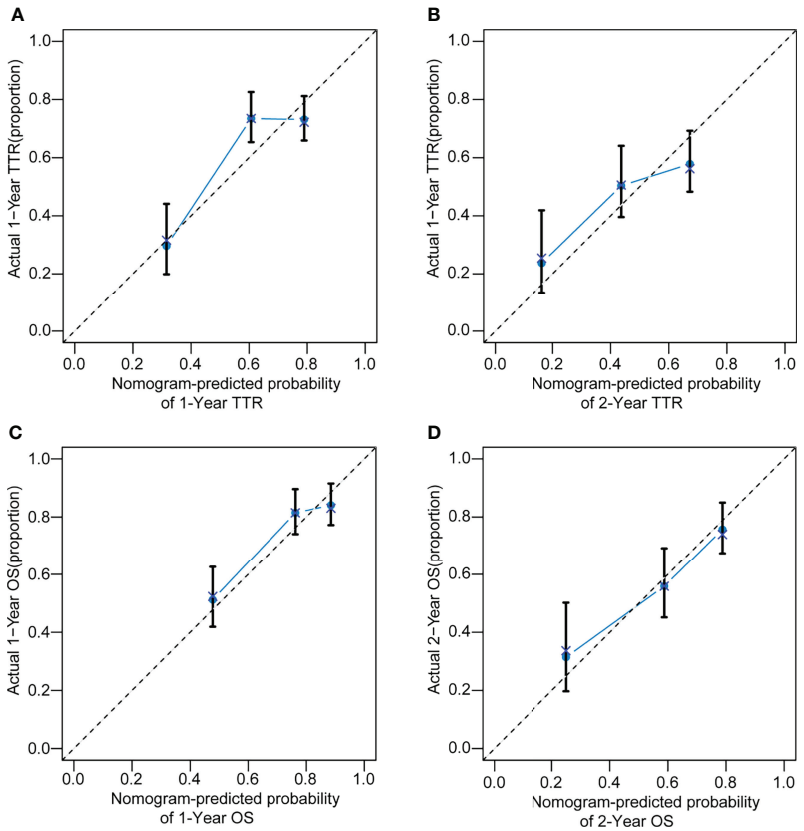

FIGURE 4 | The calibration curve for predicting TTR at 1 years **(A)**, 2 years **(B)** and OS at 1 years **(C)**, 2 years **(D)** in HCC patients with MVI after radical resection.

147 HCC patients with MVI who received adjuvant sorafenib after R0 resection showed 1-, 3-, and 5-year tumor-free survival and OS rates of 66.0%, 40.0%, 24.0% and 70.0%, 54.0%, 43.0%, respectively, which were significantly improved compared with those observed in patients who had not received postoperative adjuvant sorafenib (P=0.029, P=0.003, respectively). Similar results were described after PSM (13).

Lenvatinib has been found to have non-inferior efficacy to sorafenib in untreated advanced HCC (7). It is considered the best treatment option for HBV-related HCC due to the lowest HR compared with sorafenib (HR 0.83, 95% CI 0.68-1.01), although the reasons for the divergent responses by viral etiology remain unclear (32). Several studies have reported that lenvatinib is more effective than sorafenib in treating HCC with macrovascular invasion, this may be owing to the potent activity against FGFR1–4 is a distinctive feature of lenvatinib, compared with sorafenib (33–36). According to the HCC guidelines, lenvatinib is recommended only for HCC with macrovascular invasion (10). Whether to administer lenvatinib for HCC with MVI remains controversial, even though MVI is a key factor for recurrence and metastasis after surgery. We, therefore, designed this study to investigate whether postoperative adjuvant lenvatinib treatment improves prognosis in HBV-related HCC patients with MVI.

Adjuvant treatment with lenvatinib has been shown to inhibit tumor recurrence and metastasis after liver transplantation in HBV-related HCC patients with a high risk of recurrence (37). In a study described by Han, 14 HCC patients with a high risk of recurrence who received liver transplantation followed by adjuvant lenvatinib and 9 such patients who did not receive adjuvant lenvatinib treatment were included. The results showed that the progression-free survival of the lenvatinib group was significantly better than the control group (P=0.04) (37). There has been no report elaborating the effect of adjuvant lenvatinib on the long-term survival of HCC in patients who underwent liver resection. In this study, 57 patients receiving adjuvant lenvatinib were included for recurrence and survival analysis. The results indicated that the 1-year, 2-year recurrence rates and survival rates were more favorable for the lenvatinib group compared to the non-lenvatinib group (15.9%, 43.2% vs 40.1%, 57.2%, P=0.002; 85.8%, 71.2% vs 69.2%, 53.3%, P=0.009, respectively). After elimination of potential bias induced by differences in baselines characteristics, PSM was implemented and similar findings were observed compared to those before PSM. The 1-, 2-year recurrence rates and survival rates of the lenvatinib group were improved compared to the non-lenvatinib group (15.9%, 43.2% vs 42.1%, 57.4%,

P=0.028; 85.8%, 71.2% vs 70.0%, 53.4%, P=0.024, respectively). As shown by univariate and multivariate analyses, absence of adjuvant lenvatinib treatment has been identified as independent risk factors for recurrence and survival. Additionally, nomograms were established based on these independent risk factors, which displayed good prediction performance.

This study has some limitations. First of all, this study is a single-center retrospective trial, and multi-center, large sample studies are still needed to further confirm the findings. Next, the data on 3-year survival was not available due to relatively short duration of follow-up. We will increase our sample size and extend the duration of follow-up in our future studies. Additionally, this study was conducted in China and included only patients with underlying condition of HBV infection. Thus the findings warrant further validation from study cohorts with hepatitis C virus infection or alcoholic or non-alcoholic fatty liver disease as the dominant pathology of HCC.

CONCLUSIONS

In conclusion, the study demonstrated that postoperative adjuvant lenvatinib therapy could improve the long-term prognosis after R0 resection in HBV-related HCC patients with MVI, which could be accurately predicted based on the established nomograms. However, the findings of this study warrant further validation by conducting multicenter randomized controlled trials of large sample size.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was approved by the Institutional Ethics Committee of the hospital and each patient signed the informed consent to collect his/her data for the purpose of the study.

AUTHOR CONTRIBUTIONS

Study concept and design: SB, JL, FX and YS. Acquisition, analysis, or interpretation of data: SB, JL and MS. Statistical analysis: SB. Critical revision of the manuscript for important intellectual content: FX and YS. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.919824/full#supplementary-material

Supplementary Figure 1 | Flow Chart of patient's inclusion

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Indocyanine green fluorescence-guided laparoscopic hepatectomy versus conventional laparoscopic hepatectomy for hepatocellular carcinoma: A single-center propensity score matching study

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Background: Indocyanine green fluorescence-guided laparoscopic hepatectomy (ICG-guided LH) is increasingly used for the treatment of hepatocellular carcinoma (HCC). However, whether ICG-guided LH can improve surgical outcomes remains unclear. This study aimed to investigate the short-term outcomes and survival outcomes of ICG-guided LH versus common laparoscopic hepatectomy (CLH) for HCC.

Methods: We conducted a retrospective analysis of 104 ICG-guided LH and 158 CLH patients from 2014 to 2020 at our center. To avoid selection bias, 81 ICG-guided LH and 81 CLH cases were analyzed after 1:1 propensity score matching (PSM). The baseline data and results were compared between the two groups.

Results: The baseline characteristics of both groups were comparable after matching. There was a significant difference in operative time: longer in the ICG-guided LH group than in the CLH group (p=0.004). However, there was no significant difference in operative time in anatomical resection between the two groups (p=0.987). There was a significant difference in operative time in non-anatomical resection: longer in the ICG-guided LH group than in the CLH group (p=0.001). There were no significant differences in positive surgery margin, blood loss, blood transfusion rate, postoperative complication rate, postoperative length of hospital stay, mortality within 30 days, and mortality within 90 days. The ICG-guided LH group appeared to have a trend towards

better overall survival (OS), but there was no significant difference in OS (P=0.168) and recurrence-free survival (RFS) (P=0.322) between the two groups.

Conclusions: Although ICG fluorescence-guided LH is a timelier procedure to perform, it is a safe and effective technique with the advantages of intraoperative positioning, low postoperative complication rates, and potential to improve OS.

KEYWORDS

indocyanine green, laparoscopy, hepatectomy, outcomes, hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) was one of the most common cancers worldwide in 2020 (1). Although new drugs and trials for advanced HCC have developed rapidly in the past few years (2), there are still limited methods to cure early HCC, which include liver resection, liver transplantation and local ablation therapies. Unfortunately, local ablation therapies have been reported to have shorter recurrence-free survival (RFS) than liver resection (3), and liver transplantation is limited, leaving liver resection as the primary radical treatment for early HCC. In the past ten years, the application of laparoscopic hepatectomy (LH) has been popular all over the world (4), especially in large expert centers. In contrast to open hepatectomy, LH seems to have similar oncological survival outcomes, shorter hospital stay, less blood loss and less operative morbidity (5, 6). To better judge the boundary of the tumor and the extent of resection during laparoscopic surgery, indocyanine green (ICG) fluorescence navigation has been applied during laparoscopy. Through intraoperative real-time fluorescence navigation, R0 resection can be achieved, and the tumor can be completely removed while preserving as much of the liver as possible. ICG fluorescence navigation also has a positive effect on the detection of small liver cancer (7). ICG fluorescence navigation can help identify the ductal system of the liver during surgery, which may help identify intraoperative bile leakage and reduce the occurrence of postoperative bile leakage (8, 9).

However, whether indocyanine green fluorescence-guided laparoscopic hepatectomy (ICG-guided LH) or liver resection have an advantage in survival rate remains unclear. Previous studies have suggested less blood loss, less intraoperative blood transfusion rate, shorter operation time, shorter hospital stay and lower complication rate during surgery with ICG fluorescence navigation (5, 6, 10–14). These studies mostly involved only a few cases and lacked propensity score matching (PSM) and prognostic data (15). Several meta-analyses have been conducted on this topic. Qi et al. (16, 17) reported that the ICG fluorescence imaging-guided hepatectomy group had different results in operative time, blood loss, blood transfusion rate, hospital stay and postoperative complications compared with the traditional hepatectomy group. Yu Liu et al. (18) showed that ICG fluorescence imaging-guided hepatectomy shortened operative time, reduced intraoperative bleeding, shortened hospital stay and lowered postoperative complication rates. In summary, ICG-guided LH was superior to non-ICG imaging-guided hepatectomy. Furthermore, additional matched cohorts and systematic reviews should be conducted to support these findings.

To provide more evidence in ICG-guided LH, we conducted this study using 1:1 PSM to compare the short-term outcomes and survival results of ICG-guided LH versus common laparoscopic hepatectomy (CLH) for HCC.

Methods

Study participants

We retrospectively collected data from patients pathologically diagnosed with HCC. A total of 289 patients, including 173 CLH and 116 ICG-guided LH cases, were enrolled in this study. All patients underwent LH from 2014 to 2020 in the Guangdong Provincial People's Hospital with an ECOG-PS score of 0-2. Patients who underwent ICG-guided laparoscopic non-anatomical hepatectomy received an intravenous injection of 0.5 mg/KG ICG 3-5 days before surgery (Video 1). In contrast, patients who underwent ICG-guided laparoscopic anatomical hepatectomy were either injected with 5-10 ml of ICG (0.025 mg/ml) into the tumor-feeding portal branch using intraoperative ultrasound or with 1 ml of ICG (2.5 mg/ml) systemically after blocking the Glissonean pedicle of the tumor. These processes are referred to as positive staining (Video 2) and negative staining (Video 3), respectively. After application of the exclusion criteria and 1:1 PSM,

81 ICG-guided LH and 81 CLH cases were compared. The study complies with the Declaration of Helsinki and was reviewed and approved in writing by the Ethics Review Institution of Guangdong Provincial People's Hospital, and an application to the ethics committee for waiver of patient informed consent has been made.

Inclusion and exclusion criteria

The patient inclusion criteria was as follows: (I) a diagnosis of HCC according to postoperative pathology and (II) operation performed laparoscopically. The exclusion criteria were as follows: (I) patients who had undergone surgical hepatectomy before confirmation of postoperative pathology for HCC, (II) conversion from LH to open hepatectomy and (III) non-radical resection. Patients who had (IV) incomplete information were also excluded.

Data collection

The information that was obtained from patients in this study included baseline information, intraoperative conditions, pathology and postoperative conditions. The baseline data that was collected included sex, age, weight, preoperative treatment, comorbidities, evaluation of New York Heart Association (NAYA), American Society of Anesthesiologists (ASA), Child-Pugh and Barcelona Clinic Liver Cancer (BCLC), tumor size, tumor number, hepatitis, cirrhosis, ascites, portal hypertension, tumor thrombus, total bilirubin, albumin, alpha-fetoprotein and prothrombin time. Intraoperative conditions included the surgical method, blood loss, operative time and blood transfusion rate. Pathology included the degree of differentiation, surgical margin, cirrhosis, macrovascular invasion and microvascular invasion (MVI). Postoperative conditions included postoperative complications, length of stay, mortality, postoperative treatment, overall survival (OS) and RFS. Most information came from the physician management system, consisting of hospital records, surgical records, anesthesia records, doctors' advice, imaging results, etc. Information on OS and RFS was obtained from regular follow-up by telephone.

Data definition

Patients treated with hepatic arterial chemoembolization, local ablation therapies, targeted therapy or immunity therapy before surgery were recognized as having undergone preoperative treatment Patients with an additional malignant tumor were defined as those with a history of tumors. Tumor size was defined as a long trial when there was only one isolated tumor or an add-up long trial when there were two or more isolated tumors measured by videography before surgery. Cirrhosis, tumor thrombus, ascites and portal hypertension were also assessed using videography. The NAYA and ASA classifications were evaluated in anesthesia records by anesthetists. Blood loss and operative time were accurately recorded in anesthesia records. Surgical methods and blood transfusion rates were checked in surgical records. OS was defined as the time from surgery to death or last follow-up. RFS was defined as the time from surgery to the day recurrence was diagnosed using videography.

Propensity score matching

Univariate analysis was used to assess the baseline comparability of the two groups. Multivariate analysis was used to identify possible factors contributing to OS and RFS. Unbalanced baseline and possible factors according to the results of univariate analysis and multivariate analysis were put into the 1:1 PSM. This was conducted using logistic regression according to a "optimal-neighbor matching" method. After 1:1 PSM, the baseline and mentioned possible factors were re-evaluated between the two groups.

Statistical analyses

Statistical analyses were conducted using Statistical Product and Service Solutions (SPSS) version 26.0. OS and RFS charts were drawn using GraphPad Prism version 9.3.1.471. In descriptive statistics, categorical data are presented as absolute numbers and proportions, while continuous variables are presented as medians and quartiles. For hypothetical statistics, categorical data were compared using the Pearson chi-square test, continuity correction or Mann-Whitney U test, while continuous variables were compared using the Mann-Whitney U test. OS and RFS were analyzed using the Kaplan-Meier method and compared using the log-rank test. Statistical significance was set at $P < 0.05$.

Results

Baseline characteristics before PSM

From January 2014 to December 2020, 289 laparoscopic hepatectomies were performed for HCC management. After exclusion, 104 ICG-guided LH and 158 CLH cases were statistically compared. Before 1:1 PSM, baseline characteristics were comparable between the groups, apart from albumin, which was less in the CLH group compared with the ICG-guided LH group [37.75 (35.49-40.13) vs. 39.25 (36.73-41.75); p=0.008]. For Child-Pugh classification, more patients presented with Child-Pugh B or C in the CLH group than in the ICG-

guided LH group [n=13 (8.20%) vs. n=0 (0%); p=0.003]. There were also more patients with hepatitis C in the CLH group than in the ICG-guided LH group [n=18 (11.4%) vs. n=4 (3.8%); p=0.031]. Regarding the degree of differentiation [p=0.016] and postoperative treatment, there were more patients with postoperative treatment in the CLH group than in the ICG-guided LH group [n=65 (41.1%) vs. n=22 (21.2%); p=0.001]. Finally, there were more patients with postoperative Transcatheter Arterial Chemoembolization (TACE) or Hepatic Artery Infusion Chemotherapy (HAIC) in the CLH group than in the ICG-guided LH group [n=49 (31%) vs. n=11 (10.6%); p=0.000]. The details are presented in Table 1.

Univariate and multivariate analysis of OS and RFS

Before 1:1 PSM, univariate analysis showed that the degree of differentiation (P=0.003) and targeted therapy or immunotherapy (P=0.047) were correlated with OS. Sex (P=0.009), age (P=0.031), alpha-fetoprotein (P=0.005), HBV (P=0.046), postoperative treatment (P=0.003), postoperative surgery (P=0.041), tumor size (P=0.046) and MVI (P=0.005) were correlated with RFS.

Baseline characteristics after PSM

Sex, age, degree of differentiation, AFP, ALB, HBV, HCV, Child-Pugh score, tumor number, surgical method, MVI, postoperative treatment, postoperative surgery, postoperative TACE or HAIC and postoperative drugs were included as predictors in the PSM. After 1:1 PSM, 81 ICG-guided LH and 81 CLH were compared. Baseline characteristics were comparable between the 81 ICG-guided LH and 81 CLH groups. The details are showed in Table 1.

Comparison of short-term outcomes and survival results after PSM

The baseline characteristics of both groups were comparable after matching. The statistical details of short-term outcomes are shown in Table 2. There was a statistically significant difference in operative time that was longer in the ICG-guided LH group than in the CLH group [268 min (222.5-322.5) vs 230 min (167.5-285); p=0.004]. There was no significant difference in operative time in anatomical resection between the two groups (p=0.987), while there was a significant difference in operative time in non-anatomical resection that was shown to be longer in the ICG-guided LH group than in the CLH group (p=0.001). There were no significant difference of positive surgery margin [n=1 (1.2%)] in the CLH group compared with that in the ICG-guided LH group (p=1), nor were there significant differences in blood loss [100 ml (50-450) in the CLH group versus 200 ml (100-400) in the ICG-guided LH group (p=0.319)], blood transfusion rate [n=9 (11.1%) in the CLH group versus n=5 (6.2%) in the ICG-guided LH group (p = 0.263)], postoperative bleeding [n=0 (0%) in the CLH group versus n=2 (2.5%) in the ICG-guided LH group (p=0.477)], bile leakage [n=0 (0%) in the CLH group versus n=0 (0%) in the ICG-guided LH group (p=1)], liver failure [n=2 (2.5%) in the CLH group versus n=2 (2.5%) in the ICG-guided LH group] and postoperative length of stay [7 days (6-8) in the CLH group versus 7 days (6-10) in the ICG-guided LH group (p=0.081)]. There was also no significant difference in mortality within 30 days between the two groups [n=0 (0%) in the CLH group versus n=1 (1.2%) in the ICG-guided LH group (p=1) and mortality within 90 days [n=1 (1.2%) in the CLH group versus n=2 (2.5%) in the ICG-guided LH group (p =1)].

Overall and recurrence-free survival before and after PSM

Before 1:1 PSM, there was significant difference in OS (P=0.0378) while there was no significant difference in RFS (P=0.684) between the two groups (Figure 1). After 1:1 PSM, the median follow-up time was 46 months in the CLH group and 26 months in the ICG-guided LH group (P=0.000). The ICG-guided LH group appeared to have a trend towards better OS, but there was no significant difference in OS (P=0.168) and RFS (P=0.322) between the two groups (Figure 1). The 1-, 2-, 3- and 4-year OS rates were 93.5%, 90.8%, 80.9% and 77%, respectively, in the CLH group and 96.1%, 92.2%, 89.6% and 80.6%, respectively, in the ICG-guided LH group. The 1-, 2-, 3- and 4-year RFS rates were 81.6%, 75.6%, 72.0% and 67.9%, respectively, in the CLH group and 86.5%, 69.7%, 58.7% and 44%, respectively, in the ICG-guided LH group.

Discussion

Laparoscopic liver resection has been shown to be a safe and minimally invasive surgical procedure (19). Fluorescence laparoscopy has overcome difficulties associated with laparoscopic surgery, such as tumor localization for the treatment of liver malignant tumors and is expected to improve perioperative indicators and long-term prognosis (20, 21).

Indocyanine green fluorescence aids intraoperative tumor identification

Hepatocytes can take up and excrete ICG, and the tumor site is stained owing to abnormal excretion; therefore, the tumor can be specifically visualized (22). By intravenous injection of 0.5

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TABLE 1 Comparison between baseline characteristics.

	unmatched cohort			1:1 Propensity score matching		
	LH (n=158)	**ICG-guided LH (n=104)**	**p value**	**LH** (n=81)	**ICG-guided** LH (n=81)	**p value**
Sex, n (%)			0.681			0.828
Male	138 (87.3)	89 (86.6)		69 (85.2)	68 (84)	
Female	20 (12.7)	15 (13.4)		12 (14.8)	13 (16)	
Age, n(%), years			0.092			0.397
≤49	52 (32.9)	28(26.9)		26 (32.1)	25 (30.9)	
50-59	49 (31)	25 (24)		25 (30.9)	17 (21)	
60-69	38 (24.1)	36 (34.6)		20 (24.7)	28 (34.6)	
≥70	19 (12)	15 (14)		10 (12.3)	11 (13.6)	
Weight, median (IQR), kg	65 (59.8- 70.3)	64 (56-70)	0.238	66 (60-71.8)	64 (57-70)	0.125
Preoperative treatment						
TACE or HAIC, n(%)	7 (4.4)	4 (4.9)	1	3 (3.7)	4 (4.9)	
local ablation, n(%)	2 (1.3)	1 (0.96)	0.67	0 (0)	0 (0)	1
Comorbidities						
Hypertension,n(%)	37 (23.4)	27 (26)	0.639	17 (21)	22 (27.2)	0.358
Diabetes, n(%)	19 (12)	11 (10.6)	0.719	10 (12.3)	9 (11.1)	0.807
Coronary heart disease, n(%)	4 (2.5)	3 (2.9)	1	1 (1.2)	3 (3.7)	0.613
History of tumor, n(%)						
	6 (3.8)	3 (2.9)	0.96	4 (4.9)	2 (2.5)	0.677
Evaluation						
NYHA, n(%)			0.604			0.396
I	103 (65.2)	64 (61.5)		55 (67.9)	49(60.5)	
II	53 (33.5)	40 (38.5)		24 (29.6)	32 (39.5)	
III	2 (1.3)	0 (0)		2 (2.5)	0 (0)	
ASA, n(%)			0.112			0.228
I	25 (15.8)	11 (10.6)		16 (19.8)	8 (9.9)	
II	124 (78.5)	83 (79.8)		58 (71.6)	67,(82.7)	
III	9 (5.7)	10 (9.6)		7 (8.6)	6(7.4)	
Child-Pugh, n(%)			0.003			1
A	145 (91.8)	104 (100)		81 (100)	81 (100)	
B	12 (7.6)	0 (0)		0 (0)	0 (0)	
C	1(0.6)	0 (0)		0 (0)	0 (0)	
BCLC, n(%)			0.318			0.467
0	27 (17.1)	15 (14.4)		15 (18.5)	11 (13.6)	
A	124 (78.5)	81 (77.9)		62 (76.5)	66 (81.5)	
B	6 (3.8)	7 (6.7)		3 (3.7)	3 (3.7)	
C	1 (0.6)	1 (1.0)		1 (1.2)	1 (1.2)	
Liver condition						
Hepatitis B, n(%)	129 (81.6)	93 (89.4)	0.087	74 (91.4)	73 (90.1)	0.786
Hepatitis C, n(%)	18(11.4)	4 (3.8)	0.031	4 (4.9)	4 (4.9)	1
Imaging Cirrhosis, n(%)	62 (39.2)	31 (29.8)	0.118	26 (32.1)	27 (33.3)	0.867
Portal hypertension, n(%)	26 (16.5)	17 (16.3)	0.981	9 (11.1)	15 (18.5)	0.185
Tumor thrombus, n(%)	1(0.6)	1 (1)	1	1 (1.2)	1 (1.2)	1
Ascites, n(%)	3 (1.9)	3(2.9)	0.92	0 (0)	3 (3.7)	0.244
Tumor condition						
Tumor size, median (IQR), mm	32.5 (23-47)	35.5 (23-53)	0.401	30 (22-50.5)	35 (23-54)	0.354
<50	122 (77.2)	73 (70.2)	0.241	59 (72.8)	57 (70.4)	0.811

(Continued)

TABLE 1 Continued

	unmatched cohort			1:1 Propensity score matching		
50-100	32 (20.3)	30 (28.8)		19 (23.5)	23 (28.4)	
>100	4 (2.5)	1 (1)		3 (3.7)	1 (1.2)	
Tumor number, n(%)						0.213
1	151 (95.6)	93 (89.4)	0.059	78 (96.3)	74 (91.4)	
2	4 (2.5)	9 (8.7)		1 (1.2)	2 (8.6)	
3	1 (0.6)	0 (0)		0 (0)	0 (0)	
>3	2 (1.3)	2 (1.9)		2 (2.5)	0 (0)	
Grade, n(%)			0.016			0.88
Well-differentiated	9 (5.7)	6 (5.8)		7 (8..6)	4(4.9)	
Moderately differentiated	147 (93)	98 (94.2)		44 (54.3)	48 (59.3)	
Poorly differentiated	2 (1.3)	0 (0)		30 (37)	29 (35.8)	
Macrovascular invasion, n(%)	0 (0)	1 (1)	0.833	0 (0)	1 (1.2)	1
Microvascular invasion, n(%)	30 (19)	17 (16.3)	0.586	14 (17.3)	16 (19.8)	0.686
Pathologically Cirrhosis , n(%)	82 (51.9)	46 (44.2)	0.224	43 (53.1)	40 (49.4)	0.637
Postoperative treatment						
Treatment, n(%)	65 (41.1)	22 (21.2)	0.001	20 (24.7)	2 0(24.7)	1
Surgery, n(%)	17 (10.8)	6 (5.8)	0.163	4 (4.9)	6 (7.4)	0.514
TACE or HAIC, n(%)	49 (31)	11 (10.6)	0	13 (16)	11 (13.6)	0.658
Drugs, n(%)	6 (3.8)	2 (1.9)	0.62	0 (0)	0(0)	1
Total bilirubin, median (IQR),umol/L	15.0(11.5-18.8)	14.1 (10.7-17.7)	0.12	15.1 (11.7-18.7)	13.4 (10.5-18.0)	0.136
Albumin, median (IQR), g/L	37.8 (35.5-40.1)	39.3 (36.7-41.8)	0.008	38.9 (36.8-40.8)	39 (35.5-41.3)	0.758
Alpha-fetoprotein, median (IQR), ng/ml	24.8 (4.2-275.1)	15.0 (4.2-280.9	0.632	14.2 (3.8-311.7)	16.1 (4.3-273.7)	0.769
Prothrombin time, median (IQR), sec	13.8 (13.2-14.4)	13.8 (13.2-14.4)	0.868	13.8 (13.2-14.5)	13.8 (13.2-14.7)	0.619
Surgical method, n(%)			0.424			0.452
Right hepatectomy	6 (3.8)	2 (1.9)		4 (4.9)	2 (2.5)	
Left hepatectomy	5 (3.2)	4 (3.4)		3 (3.7)	3 (3.7)	
Extended left hepatectomy	1 (0.6)	1 (1.0)		1 (1.2)	0(0)	
Left lateral sectionectomy	13 (8.2)	9 (8.7)		9 (11.1)	4 (4.9)	
Anatomical segmentectomy	1 (0.6)	9 (8.7)		1 (1.2)	7 (8.6)	
Right anterior hepatectomy	1 (0.6)	1 (1.0)		0 (0)	0 (0)	
right posterior hepatectomy	0 (0)	2 (1.9)		0 (0)	1 (1.2)	
Wedge resection	131 (82.9)	76 (73.1)		63 (77.8)	64 (50.4)	

*Statistical significance was set at $P < 0.05$.

mg/kg ICG 3-7 days before surgery, a circle of fluorescence around the liver cancer can be seen during surgery, which aids in immediately identifying superficial tumors (23, 24). Compared with intraoperative ultrasound, ICG fluorescence can help the chief surgeon find the specific location of the tumor faster and determine the extent of tumor resection (25).

Previous studies by our team have shown that fluoroscopy provides more precise information on tumor location than intraoperative ultrasound, particularly for sites of difficult liver segments (24). Although there are no valid statistical data in this study to prove the localization effect of ICG, such as shortening the operation time, in some cases we observed some lesions that were not detected on preoperative imaging. After surgical resection of these lesions, the postoperative pathology report was HCC. We are greatly encouraged by the ability of fluoroscopy to detect imaging-negative HCC, demonstrating that fluoroscopy is a promising laparoscopic technique. In cases of small superficial tumors, fluoroscopy can quickly identify the lesions during the operation, which greatly shortens the operation time.

Indocyanine green fluorescence helps reduce intraoperative bleeding

Blood loss during laparoscopy is greatly reduced compared with that during open surgery (26, 27). Through preoperative three-dimensional reconstruction and intraoperative ICG, the relationship

TABLE 2 Comparison between short-term outcomes and survival outcomes.

	unmatched cohort			1:1 Propensity score matching		
	LH (n=158)	ICG-guided LH (n=104)	P value	LH (n=81)	ICG-guided LH (n=81)	p value
Surgery margin, n (%)	1 (0.6)	2 (1.9)	0.714	1 (1.2)	1 (1.2)	1
Operative time, median (IQR),min	229.5 (180-285.8)	268 (211.3-328.8)	0.008	230 (167.5-285)	268 (222.5-322.5)	0.004
anatomical resection						0.9870
non-anatomical resection						0.001
Blood loss						
Blood loss, median (IQR),ml	100 (50-400)	175 (50-400)	0.159	100 (50-450)	200 (100-400)	0.319
<400ml	123 (77.8)	80 (76.9)	0.861	61 (75.3)	63 (77.8)	
>400ml	35 (22.2)	24 (23.1)		20 (24.7)	18 (22.2)	0.711
Blood transfusion rate, n (%)	18 (11.4)	8 (7.7)	0.327	9 (11.1)	5 (6.2)	0.263
Postoperative length of stay, median (IQR),days	7 (6-9)	7 (6-10)	0.675	7 (6-8)	7 (6-10)	0.081
Complication						
bleeding, n (%)	2 (1.3)	3 (2.9)	0.634	0 (0)	2 (2.5)	0.477
Biliary fistula, n (%)	1 (0.6)	1 (1)	1	0 (0)	0 (0)	1
Liver failure, n (%)			0.143			0.333
PHLF A	4 (2.5)	0 (0)		2 (2.5)	0 (0)	
PHLF B	1 (0.6)	0 (0)		0 (0)	0 (0)	
PHLF C	1 (0.6)	2 (1.9)		0 (0)	2 (2.5)	
Clavien-Dindo			0.643			0.141
Classification 1	9 (5.7)	5 (4.8)		2 (2.5)	3 (3.7)	
Classification 2	0 (0)	1 (1.0)		0 (0)	1 (1.2)	
Classification 3	0 (0)	1 (1.0)		0 (0)	1 (1.2)	
Classification 4	1 (0.6)	1 (1.0)		0 (0)	1 (1.2)	
Prognosis						
Mortality within 30 days, n (%)	2 (1.3)	1 (1)	1	0 (0)	1 (1.2)	1
Mortality within 90 days, n (%)	3 (1.9)	2 (1.9)	1	1 (1.2)	2 (2.5)	1
1-year RFS, (%)	0.797	0.874		0.816	0.865	
2-year RFS, (%)	0.696	0.711		0.756	0.697	
3-year RFS, (%)	0.624	0.627		0.72	0.587	
4-year RFS, (%)	0.569	0.522		0.679	0.44	
1-year OS, (%)	0.922	0.972		0.935	0.961	
2-Year OS, (%)	0.865	0.937		0.908	0.922	
3-Year OS, (%)	0.789	0.915s		0.809	0.896	
4-Year OS, (%)	0.769	0.832		0.77	0.806	

*Statistical significance was set at $P < 0.05$.

between large blood vessels and tumors can be fully identified and the possibility of major bleeding can be reduced, thereby reducing intraoperative bleeding (28). Intraoperative blocking of the hepatic hilum can reduce intraoperative bleeding and clarify the operative field (29, 30). Other laparoscopic techniques, including appropriate pneumoperitoneum pressure and low central venous pressure, can also reduce intraoperative bleeding (31, 32).

Previous studies have reported that ICG can reduce intraoperative blood loss (15). Herein, we report a case that supports these results. Preoperative enhanced CT showed malignant lesions in the S4 and S2 segments of the liver, with diameters of 6 cm and 5 cm, respectively. The surgery was performed on February 27, 2018. Intraoperative exploration was consistent with preoperative imaging, and left hepatectomy was performed. The left hepatic pedicle was separated and clipped during the operation and the ICG was injected peripherally. The S5, S6, S7, and S8 segments were stained green. Left hepatectomy was performed according to the liver staining band, and

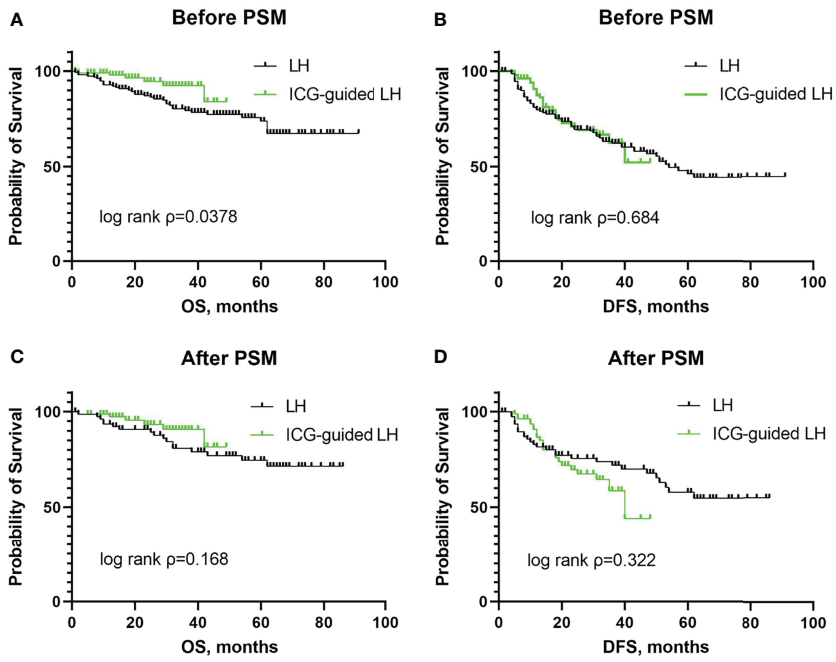

Figure 1 Comparison of survival outcomes of LH group versus ICG-guided LH group: (A) OS before PSM (B) RFS before PSM (C) OS after PSM (D) RFS after PSM

FIGURE 1
Comparison of survival outcomes of LH group versus ICG-guided LH group: **(A)** OS before PSM **(B)** RFS before PSM **(C)** OS after PSM **(D)** RFS after PSM.

intraoperative blood loss was only 80 ml. The patient survived until the last follow-up on April 30, 2021.

Our study shows that fluorescein laparoscopy is a safe laparoscopic technique with low intraoperative bleeding and intraoperative blood transfusion rates.

ICG-guided resection causes fewer severe liver failures

Postoperative primary liver failure is the leading cause of death following hepatectomy (33). Risk factors include underlying liver disease, the extent of resection and intraoperative conditions (33). Before major hepatectomy, functional and volumetric assessments of the remnant liver are critical (34). Lack of preoperative residual liver assessment and excessive intraoperative bleeding can increase the incidence of postoperative primary liver failure (35). Large hepatectomy requiring removal of the portal vein often leads to postoperative liver failure and increases perioperative mortality, especially in patients with hepatic steatosis (36).

Fortunately, compared with traditional LH, fluoroscopy-guided LH for non-anatomical hepatectomy can ensure both R0 resection (15) and a safe margin within the 6-8 mm range (7, 37), avoiding the larger resection range brought about by anatomical hepatectomy.

In the present study, 82.9% of 262 patients underwent non-anatomical hepatectomy with conventional laparoscopy, 73.1% underwent non-anatomical hepatectomy with fluorescence laparoscopy and 98.8% underwent negative surgery margin. Only three patients (1.1%) developed severe postoperative liver failure, which was reported at low levels (1%-9%) in the literature (38); two of the three underwent anatomical hepatectomy.

ICG-guided non-anatomical resection may ensure safe surgery margin and lead to improved OS

Previous studies on HCC and fluorescence laparoscopy have rarely addressed prognosis. We know that the fluorescence border seen during surgery is not equal to the tumor border but is wider than the tumor border. This provides R0 resection and a wide incisal margin. In recent years, wide resection margins for hepatic malignancies have been associated with a better prognosis (39–42). Fluoroscopic resection of HCC is expected to improve prognosis. In the present study, the fluorescence laparoscopy group appeared to have better OS.

Limitation

Our study had some limitations. Firstly, the follow-up time of the ICG-guided LH group was not long enough, resulting in a significant difference in the follow-up time between the two groups. Secondly, we collected data retrospectively, and the retrospective study was more biased. Thirdly, the sample size was small; increasing the sample size may make the results statistically different. Fourthly, the number of positive events was small. For example, the number of cases of bile leakage was small, which resulted in the differences being insignificant.

Conclusion

Although ICG fluorescence-guided LH is a timelier procedure to perform, it is a safe and effective technique with the advantages of intraoperative positioning, low postoperative complication rates and the potential to improve OS.

Data availability statement

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

Ethics statement

Ethical approval was not provided for this study on human participants because Retrospective analysis may apply for exemption from ethical review. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

WJ and ZX collected the related data and completed the manuscript and figures. ZZH, ZZ, and PT did the statistical analysis. LY, JH, JZ, and WH did the operations. WH gave constructive guidance and made critical revisions of the manuscript. WJ and WH participated in the design of this paper. 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.2022.930065/full#supplementary-material.

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Case report: Conversion therapy for advanced intrahepatic cholangiocarcinoma using PD-1 inhibitor plus S-1 and nab-paclitaxel

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Intrahepatic cholangiocarcinoma (iCCA) is a highly malignant hepatobiliary tumor with a high rate of advanced disease at initial presentation. Conversion into resectable iCCA is important for improving the prognosis. Immunotherapy-based regimens are being increasingly used for treating advanced iCCA in recent years. However, the use of combined chemotherapy and immunotherapy for conversion has rarely been reported. The aim of this report was to present the outcomes of a 52-year-old female patient with IIIB iCCA. The patient was treated with a programmed cell death protein-1 inhibitor plus S-1 and nab-paclitaxel. The postoperative histopathological results indicated pathologic complete response after six cycles of systematic treatment. The patient is currently disease-free for one year.

KEYWORDS

intrahepatic cholangiocarcinoma, case report, conversion therapy, complete remission, immunotherapy combined therapy

Introduction

Intrahepatic cholangiocarcinoma (iCCA) is the second most common liver malignancy after hepatocellular carcinoma (1); it is a highly malignant hepatobiliary tumor with an increasing incidence (2). Most of cases of iCCA are diagnosed in advanced stages at presentation, with a median survival of less than one

year. Most patients are therefore no longer eligible for radical surgery, and chemotherapy forms an important part of treatment.

First-line chemotherapy for advanced iCCA includes gemcitabine, a platinum derivative, nab-paclitaxel, and fluoropyrimidines (3). However, only a few chemotherapy studies on chemotherapy were designed for iCCA alone. The BILCAP study compared capecitabine with observation following resection in patients with biliary tract cancer patients following resection. The median overall survival was prolonged from 36 months to 53 months in the capecitabine group (4). The ABC-06 study randomly compared folinic acid, fluorouracil, and oxaliplatin chemotherapy (FOLFOX) plus active symptom control with active symptom control alone as a second-line treatment for biliary tract cancer patients following cisplatin and gemcitabine failure (5). The results indicated that the FOLFOX regimen improved the overall survival rate by 14.5% at 12 months. In recent years, programmed cell death protein-1 (PD-1) inhibitors have shown effectiveness in conversion therapy for advanced liver cancer (6–9). An increasing number of studies are reporting promising outcomes with immunotherapy plus chemotherapy or targeted therapy for advanced liver cancer (10–17). Research indicates that iCCA has a rich tumor stroma; this suggests that immunotherapy may offer benefits in this tumor (18, 19). However, the outcomes with immunotherapy have been found to be unsatisfactory (19). Different studies indicate that chemotherapy, and especially 5-FU analogues, could upregulate programmed cell death ligand-1 (PD-L1) expression in tumor tissue and enhance the therapeutic effect of immunotherapy (20–26). However, the clinical benefit of immunotherapy plus chemotherapy for advanced iCCA remains unclear.

This report presents the results of a new combined regimen with chemotherapy and immunotherapy for advanced iCCA, that offered successful conversion for radical resection. The postoperative specimen showed pathological complete response according to the Response Evaluation Criteria in Solid Tumors (version 1.1). The episode of care for this patient is summarized in Figure 1A.

Case description

A 52-year-old woman was admitted to our hospital with jaundice for 6 days. She did not have a history of chronic hepatitis B or C infection. The Eastern Cooperative Oncology Group performance status score was 0. The total and direct bilirubin levels were 232.7 μmol/L and 186.1μmol/L, respectively, the alpha-fetoprotein level exceeded 1000 ng/ml, and the cancer antigen 19-9 level was 96.06 units/ml; the carcinoembryonic antigen level was within normal limits. An upper abdominal enhanced computed tomography (CT) scan showed a tumor measuring 5.8 cm in longest diameter in segment 4 of the liver. The portal vein phase indicated that the tumor had invaded the middle hepatic vein and the umbilical portion of the left portal vein and was adjacent to the main trunk of the right portal vein (Figures 1B–D). The tumor had also invaded the liver hilum, leading to biliary obstruction.

Diagnostic assessment, therapeutic intervention, follow-up, and outcomes

The patient underwent CT-guided percutaneous liver core biopsy and percutaneous transhepatic cholangiodrainage. Cytology confirmed the presence of cancer cells (Figure 2A); the results of immunohistochemical analysis were as follows: CK7 (+), CK19 (+), AFP (-), Hepatocyte (-), VILLIN (+), MOC-31 (+), GATA-3(-), CD34 (-), Glypican-3 (-), and Ki-67 labelling index: 70% (Figure 2B). According to the American Joint Committee on Cancer staging system, 8th edition, the patient was diagnosed with stage IIIB (T2N1M0) iCCA.

According to the opinion of a multidisciplinary team, she then received chemotherapy and immunotherapy after the total bilirubin had returned to the normal level following percutaneous transhepatic cholangiodrainage. After six cycles of treatment with nab-paclitaxel (200 mg, d1 and d8), S-1 (60 mg/m2, d1 to d14), and a PD-1 inhibitor (200 mg, q21 days), an enhanced CT scan showed that the longest diameter of the tumor shrank from 5.8 cm to 3.8 cm (Figures 3A–C). The treatment response was evaluated to be a partial response according to the revised Response Evaluation Criteria in Solid Tumors (version 1.1). The patient developed myelosuppression during the third cycle of chemotherapy and recovered on administration of growth factor injections. No immune-related adverse events were observed.

After surgical reassessment, the patient underwent hepatectomy (H2345'8'-B-MHV) (27), cholecystectomy, and biliodigestive anastomosis. Biliary leakage occurred on postoperative day seven and recovered after one month. No viable tumor cell was detected in the resected specimen; only necrotic tissue was detected, indicating a pathologic complete response after systematic treatment (Figure 2C). Additionally, the tissue in lymph node stations 7, 8, 9, and 12 were found to be entirely necrotic. The postoperative pathology results indicated down staging of the tumor to stage T1aN0M0 without perineural and vessel invasion; the resection margins indicated R0 resection status.

Follow-up and outcome

The patient was discharged on postoperative day 31 and monitored every 3 months for recurrence at a local hospital by CT or magnetic resonance imaging. During the recent telephonic follow-up in May 2022, the patient informed that she was living a normal daily life without any symptoms. She had

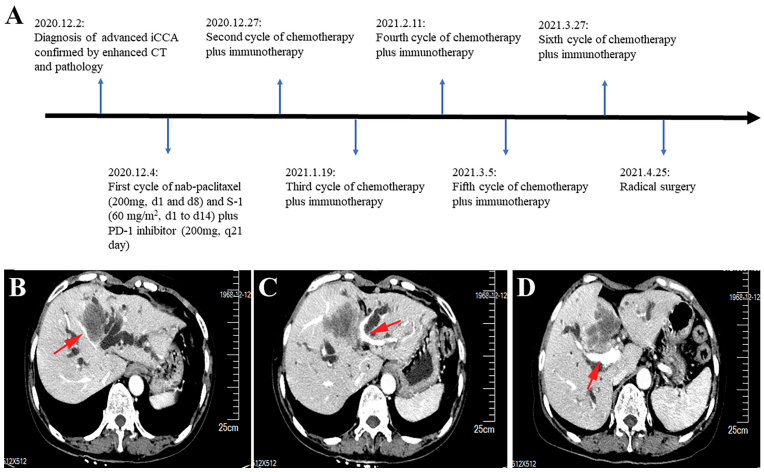

FIGURE 1
Timeline and enhanced computed tomography scan at the time of diagnosis. **(A)** Showing the course of initial diagnosis, medication, and surgery. **(B)** Showing a large mass in segment 4 of the liver invading the middle hepatic vein. **(C)** Showing the mass in segment 4 of the liver invading the umbilical portion of the left portal vein. **(D)** Showing the mass adjacent to the main trunk of the right portal vein.

therefore achieved disease-free for one year and will undergo periodic radiographic follow-up.

Discussion

To date, iCCA remains a challenging tumor without an effective treatment. Due to the highly aggressive nature of the cancer and its insidious onset, approximately 65% of cases are diagnosed in advanced stages with a median survival of less than 1 year. However, the median disease-free survival can rise up to three years after resection. Therefore, radical surgery after systemic treatment for unresectable iCCA has recently received increasing attention. The case in our study shows that conversion therapy for advanced iCCA can be achieved using a PD-1 inhibitor plus S-1 and nab-paclitaxel; this triplet regimen is safe and effective.

The patient initially presented with jaundice due to tumor compression. Preoperative biliary decompression has been traditionally performed in patients having malignant biliary obstruction with resectable tumors (28). However, growing evidence indicates that preoperative biliary decompression could increase postoperative complications (29–32). In patients with unresectable tumors, biliary decompression is necessary for improving liver function and facilitating subsequent chemotherapy. Complications associated with biliary decompression were not observed in our case.

The patient was evaluated *via* enhanced CT scans before treatment and was found to have N1 lymph node status. Lymph node dissection (LND) is recommended by the American Joint Committee on Cancer staging system, 8th edition, which suggests that at least six lymph nodes should be removed during LND (2). In this context, Kim et al. recommended that at least lymph node

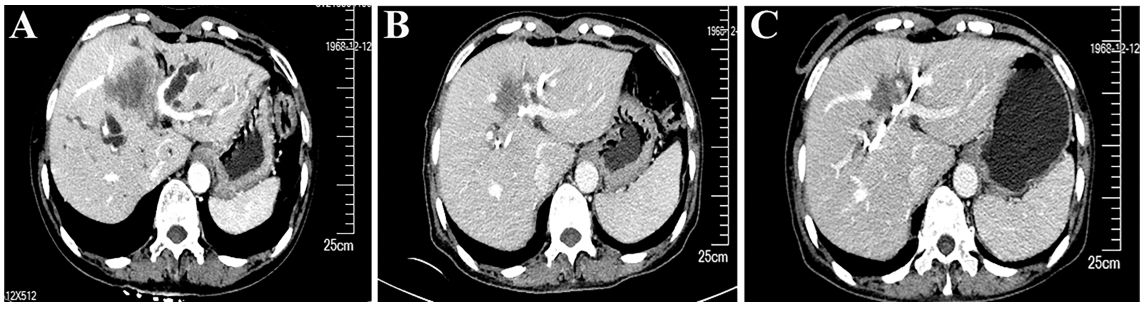

FIGURE 2
Cytologic examination and hematoxylin-eosin (HE) staining of liver tumor tissue from the needle biopsy and resected specimen. **(A)** Cytologic examination shows the presence of cancer cells (1000×). **(B)** HE staining (200×) of the liver tumor tissue from the needle biopsy. **(C)** HE staining (100×) shows only necrotic tissue in the resected tissue.

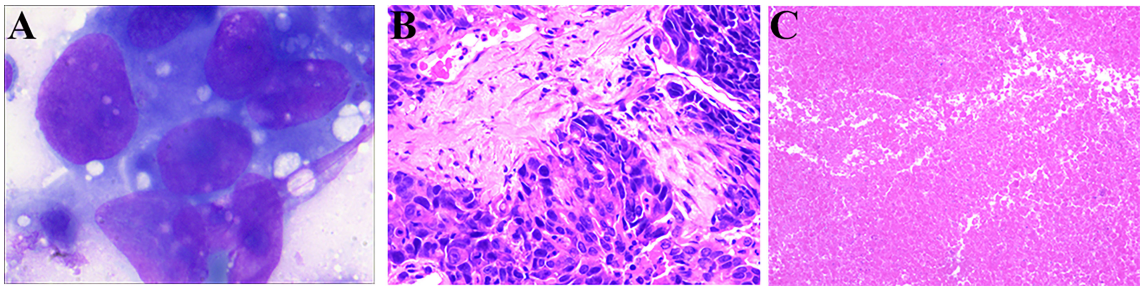

FIGURE 3
Enhanced computed tomography (CT) scans show that the cancer lesion changed over time. **(A)** CT results (2020.12.2) at the time of diagnosis. **(B)** CT results (2020.2.9) before the fourth cycle of treatment. **(C)** CT results (2020.4.23) before the radical surgery.

stations 8 and 12 should be dissected irrespective of the tumor location. Although LND is effective for evaluation of nodal status, studies are becoming increasingly skeptical about the benefits of LND for prognostication (33–35). To date, routine LND remains controversial; however, a multi-center study shows that selected patients with iCCA could benefit from LND (36).

Numerous studies on hepatocellular carcinoma have indicated that systemic conversion chemotherapy could make unresectable cases resectable (6, 7). However, conversion therapy for iCCA is relatively understudied. In a phase 2 clinical trial, nine of 41 (22%) patients with unresectable iCCA were successfully converted to surgically operable status using selective internal radiotherapy combined with chemotherapy (cisplatin and gemcitabine) (37). Riby et al. reported that 32 cases with initially unresectable iCCA in their cohort were resectable after administration of down staging chemotherapy with or without selective internal radiotherapy (38). In 2020, a French study tested FOLFIRINOX as first-line chemotherapy for advanced iCCA; 1 secondary resection was performed among 21 patients (39). In these studies, multiple chemotherapeutic agents were used to achieve good down staging. However, a combined chemotherapy regimen may be associated with severe adverse events. In another phase 2 trial, 60 patients with advanced biliary tract cancers were administered a regimen of nab-paclitaxel plus gemcitabine and cisplatin; nine (16%) patients withdrew owing to adverse events (40).

Although immunotherapy has demonstrated remarkable potency for different cancers, its efficacy in iCCA remains to be tested (41, 42). The KEYNOTE-158 study recruited 22 patients with cholangiocarcinoma who received immunotherapy; the overall response rate was 40.9% with a median progression free survival of 4.2 months (43). A phase II trial enrolled 54 patients with biliary tract cancer, including 32 cases of iCCA; the patients received at least one dose of immunotherapy and obtained a median progression free survival of 3.7 months (44).

Several ongoing studies are evaluating the efficacy of immunotherapy combined with gemcitabine with or without cisplatin; their results will be of particularly clinical value (18). In this case, we adopted a different combination of immunotherapy (PD-1 inhibitor) with S-1 plus nab-paclitaxel. S-1 is a prodrug of the active substance fluorouracil (5-FU); it can be preferentially converted to 5-FU in tumor cells (45). Studies indicate that 5-FU could induce PD-L1 expression in different cancers, including colorectal, gastric, and pancreatic cancer (20–26). Thus, we assumed that 5-FU may also upregulate PD-L1 expression in the tumor microenvironment of iCCA. The final pathological results support our hypothesis, as no active tumor cells were found in the specimen. A recent study reported a similar outcome to that of ours; in that study, a patient with advanced iCCA survived for over 16 months without progression after being treated with a PD-1 inhibitor plus capecitabine (46). Another group also successfully converted advanced iCCA to resectable status with PD-1 and tyrosine kinase inhibitors (47). These results indicate that immunotherapy may have a broader prospect in the conversion of advanced iCCA.

Although our results are promising, there are some limitations to this report. First, this report describes only one successful case; whether other patients are sensitive to this combined regimen is still unknown. A clinical trial with more patients will be needed to confirm our findings. Second, we could not test the expression level of PD-L1 due to complete necrosis of the tumor in the postoperative specimen. Further larger studies are needed to confirm whether 5-FU analogues may upregulate PD-L1 in iCCA.

Conclusion

The findings from our case suggest that our regimen (S-1 and nab-paclitaxel plus PD-1 inhibitor) is suitable for converting advanced iCCA to resectable status; this provides a new treatment choice for this tumor. However, as this report describes only one case, studies on more patients are needed to verify its effectiveness in future.

Patient perspective

When I got jaundice, I knew that something terrible happened to me. I was admitted to our local hospital and ordered a series of tests. After the results came out, the doctor asked me to transfer to the territorial central hospital. After I came to the territorial central hospital, the doctors kept encouraging me. While my jaundice improved, the doctor ordered chemotherapy and immunotherapy. At each post-treatment review, the doctor told me that the tumor was shrinking. It gave me great confidence in my treatment and made me forget the pain of chemotherapy. Finally, the doctor said to me that I was eligible for surgery. I felt a hope of rebirth. The operation was successful, and I am very grateful to the doctors. Until now, no tumor recurrence was found on postoperative monitoring. I am delighted with the treatment effect and feel confident for the future.

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.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics committee of Xiangyang Central Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XCL, XGL, XFL, YJW, and WG conceived the idea for the article. XCL and ZYJ drafted the manuscript. XGL approved the final version 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.

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Supplementary material

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Anatomical liver resection improves surgical outcomes for combined hepatocellular-cholangiocarcinoma: A propensity score matched study

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Background: The efficacies of anatomical resection (AR) and non-anatomical resection (NAR) in the treatment of combined hepatocellular-cholangiocarcinoma (cHCC-CCA) remain unclear. This study aimed to compare the prognostic outcomes of AR with those of NAR for cHCC-CCA.

Method: Patients diagnosed with pathology-confirmed cHCC-CCA, and who underwent curative resection at Tongji hospital between January 2010 and December 2019 were included in this retrospective study. A one-to-one propensity score matching (PSM) analysis was used to compare the long-term outcomes of AR to those of NAR.

Results: A total of 105 patients were analyzed, of whom 48 (45.7%) and 57 (54.3%) underwent AR and NAR, respectively. There were no significant differences in short-term outcomes between the two groups, including duration of postoperative hospital stay, the incidence of perioperative complications, and incidence of 30-day mortality. However, both, the 5-year overall survival (OS) and recurrence-free survival (RFS) rates of AR were significantly better than those of NAR (40.5% vs. 22.4%, P=0.002; and 37.3% vs. 14.4%, P=0.002, respectively). Multivariate analysis showed that NAR, multiple tumors, larger-sized tumors (>5 cm), cirrhosis, lymph node metastasis, and vascular invasion were independent risk factors for poor prognoses. Stratified analysis demonstrated similar outcomes following AR versus NAR for patients with tumors > 5cm in diameter, while AR had better survival than NAR in patients with tumors ≤5 cm in diameter. After PSM, when 34 patients from each group were matched, the 5-year OS and RFS rates of AR were still better than those of NAR.

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Conclusion: Patients with cHCC-CCA who underwent AR had better long-term surgical outcomes than those who underwent NAR, especially for those with tumors ≤5 cm in diameter. However, no differences in the risk of surgical complications were detected between the two groups.

KEYWORDS

anatomical resection, non-anatomical resection, combined hepatocellular carcinoma and cholangiocarcinoma, surgery, prognosis

Introduction

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare type of primary liver cancer that exhibits both hepatocytic and cholangiocytic differentiation within the same tumor; cHCC-CCA has an incidence rate that ranges from 0.4–14.2% and is reported to be more common in men and those with chronic liver disease (1–3). cHCC-CCA is an aggressive malignancy, with clinical and biological patterns overlapping with those of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA) (1). Due to the low incidence of cHCC-CCA, there are few published studies (mostly with low sample sizes) on the treatment and prognosis of the condition (2, 4, 5). Furthermore, there are no detailed accounts of the clinical behavior, surgical outcomes, and prognostic factors for cHCC-CCA (5–7). Compared with HCC and iCCA, standardizing treatment for cHCC-CCA is difficult due to several factors. First, it is difficult to differentiate cHCC-CCA from HCC or iCCA through imaging. Second, the incidence of cHCC-CCA is relatively low, making it difficult for a single institution to have enough patients for detailed studies. The only curative option for patients with cHCC-CCA was found to be R0 resection with lymph node dissection; however, even after radical hepatectomy or liver transplantation, long-term survival remained low (2, 4, 8, 9). The 5-year tumor recurrence rate in cHCC-CCA patients was reported to be as high as 80%, and the 5-year overall survival (OS) rates were less than 30% (10–14). High incidence rates of postoperative recurrence in cHCC-CCA patients even after curative treatment is also a major issue in the treatment of this condition.

A nationwide study in China has indicated that although cHCC-CCA reflects the malignant behavior of iCCA, it should be characterized as a subtype of HCC due to similarities in mortality rates and long-term surgical outcomes between HCC and cHCC-CCA (15). The superiority of anatomical resection (AR) over non-anatomical resection (NAR) for surgical outcomes in HCC patients is an ongoing controversy. Since cHCC-CCA has characteristics of both HCC and iCCA, the tumors have a high propensity to invade intrahepatic pedicle structures, which allows the tumor to spread *via* the closest portal veins or bile ducts. Therefore, the complete removal of tumor-bearing hepatic pedicles is considered to be ideal for surgical eradication of potential micrometastases (16). Theoretically, AR in patients with cHCC-CCA could reduce the risk of local recurrence and may improve patient survival (17). However, no reports have proved that AR is superior to NAR in treating cHCC-CCA as yet.

Therefore, this study was undertaken to clarify which—AR or NAR—is the superior treatment option based on short-term and long-term outcomes for patients with cHCC-CCA.

Patients and methods

Study population and data collection

Of the 6652 patients who underwent hepatectomy for primary hepatic malignancy between January 2010 and December 2019 at the Hepatic Surgery Center, Tongji Hospital, 118 (1.8%) were identified as having pathology-confirmed cHCC-CCA. Of these, eight were excluded due to incomplete data (including six patients who were lost to follow-up), three were excluded as exploration and biopsies confirmed that the tumors were not cHCC-CCA, and two were excluded as they had received preoperative anticancer treatments (Figure 1). The remaining 105 patients were divided into NAR (n=57) and AR groups (n=48) according to the hepatic resection they underwent.

Demographic and clinical data including age, sex, Eastern Cooperative Oncology Group-Performance status (ECOG-PS), Child classification, presence of underlying liver disease, positivity for hepatitis B viral surface antigen (HBsAg) and hepatitis C viral antibody (HCV-Ab), liver function, complete blood count, coagulation profile, tumor markers including serum α-fetoprotein (AFP), carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels were collected. Histopathological factors including the tumor size and number, vascular invasion, lymph node metastasis (LNM), and tumor stage according to the 8th edition of the Union for International

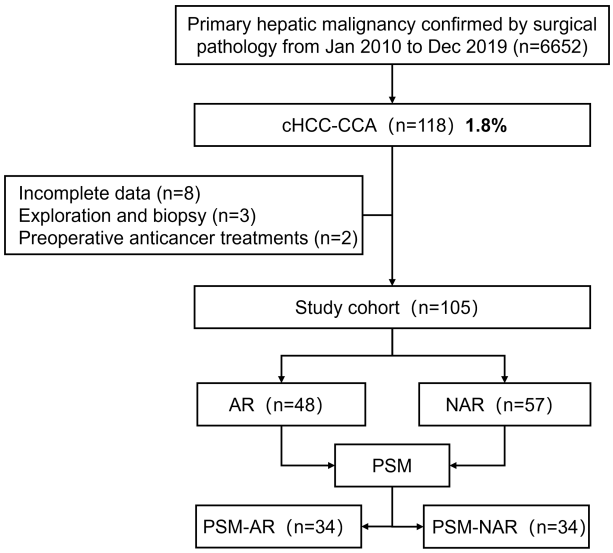

FIGURE 1
Flowchart of steps taken for patient selection for this study. *AR*, anatomical resection; *NAR*, non-anatomical resection; *PSM*, propensity score matching.

Cancer Control TNM classification (8th TNM stage) were also recorded (18).

Surgical procedures

The main surgical procedure for AR involved complete identification of the target Couinaud segment(s), following which parenchymal dissection was performed along the segmental border. Next, landmark veins were exposed on the cut surface of the liver, and the corresponding portal branches were ligated for trisectionectomy, hemihepatectomy, sectionectomy, and segmentectomy (19). For NAR (also known as conventional limited resection), the surgical procedure focused on tumor resection with a negative tumor margin regardless of segment or section anatomy. Postoperative morbidity was defined as the occurrence of complications during the hospital stay or within 3 months of resection. Complication severity was graded as per the Clavien–Dindo classification system (20).

Follow-up

Postoperative follow-up consisted of abdominal ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) along with laboratory tests to check liver function. These included checking the levels of α-fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen (CEA) every 2–3 months during the first 2 years after surgery, and then every 4–6 months thereafter. Follow-up data were collected until February 28, 2022. Recurrence-free survival (RFS) was defined as the period after the operation when no tumor recurrence could be detected by imaging or biopsy. Overall survival (OS) was the time interval between the surgery and date of death (if any).

Propensity score matching analysis

Propensity score matching (PSM) was performed to reduce biases arising from the different distributions of covariates among patients who underwent AR and those who underwent NAR. Of all the variables identified, several were significantly and independently different between the two groups. Based on these results, the following variables were included in the 1:1 PSM analysis: CEA, prothrombin time (PT), white blood cell (WBC) count, and presence of solitary tumor. To achieve the highest homogeneity, the caliper was set to 0.10.

Statistical analysis

For continuous variables, medians with inter-quartile ranges (IQR) have been reported. Such variables were compared using independent sample t-tests or Mann-Whitney U tests. Categorical variables were expressed as frequencies or percentages and compared using the Chi-square test or Fisher's exact test. Kaplan-Meier (K-M) survival curves were used to compare survival rates between the AR and NAR groups using the log-rank test. Potential risk factors associated with OS and RFS were identified using univariate and multivariable Cox

hazard regression models, and all variables with P<0.050 in the univariate analyses were utilized in multivariate analyses to determine independent risk factors. For all tests, P< 0.050 was considered statistically significant. All analyses were performed using the SSPS 24.0 software (IBM Corp., Armonk, NY, USA).

Results

Demographic and clinicopathologic characteristics

Of the 105 patients with cHCC-CCA included in this study, there were 90 (85.7%) men and 15 (14.3%) women; the mean age of the patients was 53 years (range, 28–83 years). Details regarding patient demographics, preoperative procedures, tumor characteristics, and operative procedures and care are reported in Table 1. A total of 57 patients underwent NAR (54.3%) while 48 underwent AR (45.7%). There were substantial differences in background variables between the two groups before PSM analysis. Patients in the AR group had significantly higher CEA levels and WBC counts, along with lower PT levels and smaller tumors than those in the NAR group. There were no significant differences in other clinicopathologic characteristics between the two groups. Details of the surgical procedures that the 48 patients who underwent AR are as follows: trisectionectomy (n=2);

TABLE 1 Baseline patient characteristics.

Variable	Before PSM			After PSM		
	NAR (N=57)	AR (N=48)	*P* value	PSM-NAR (N=34)	PSM-AR (N=34)	*P* value
Demographics						
Age, median (IQR), y	52(48-60)	53(46-60)	0.393	52(46-60)	52(46-57)	0.870
Sex ratio, Male: Female	48:9	42:6	0.631	29:5	30:4	1.000
Preoperative variables						
ECOG-PS, 0:1	49:8	43:5	0.768	29:5	31:3	0.709
HBsAg-positive, n (%)	36(63.2)	30(62.5)	0.945	21(61.8)	23(67.6)	0.612
HCVAb-positive, n (%)	2(3.5)	0(0)	0.499	2(3.5)	0(0)	0.499
AFP, median (IQR), μg/L	97(24-391)	74(12-502)	0.379	95(24-231)	212(12-848)	0.230
CEA, median (IQR), μg/L	3.5(2.0-4.1)	4.3(3.3-7.2)	**0.021**	3.6(2.7-4.1)	3.7(2.9-4.8)	0.882
CA-199, median (IQR), U/L	27(8-60)	37(9-75)	0.746	27(8-77)	16(6-67)	0.440
ALT, median (IQR), U/L	25(18-39)	23(18-36)	0.844	23(17-36)	28(22-30)	0.764
TBIL, median (IQR), μmol/L	10.5(7.5-15.6)	11.0(8.6-14.0)	0.827	10.7(7.2-15.1)	10.2(7.6-13.2)	0.448
ALB, median (IQR), g/L	40.2(36.4-42.9)	39.9(36.4-43.6)	0.842	40.3(36.8-44.2)	40.2(36.5-44.3)	0.844
PT, median (IQR), s	13.6(12.9-14.3)	13.1(12.8-14.0)	**0.035**	13.5(12.8-14.3)	13.1(12.9-14.0)	0.273
WBC, median (IQR), *10^9/L	5.5(4.4-6.5)	6.2(4.8-7.3)	**0.027**	5.7(4.6-6.8)	6.0(4.5-6.9)	0.756
HB, median (IQR), g/L	129(118-148)	136(124-147)	0.515	130(122-145)	136(123-147)	0.655
PLT, median (IQR), *10^9/L	184(128-237)	188(138-231)	0.868	181(123-236)	196(141-227)	0.868
Child-Pugh Class, A: B	54:3	45:3	0.828	31:3	31:3	1.000
Splenomegaly, n (%)	16(28.1)	11(22.9)	0.547	10(29.4)	9(26.5)	0.787
Tumor and operative variables						
Size, median (IQR), cm	5.7(3.5-8.3)	5.0(3.5-7.8)	0.771	6.0(3.5-9.2)	5.6(3.4-8.0)	0.532
Solitary, n (%)	40(70.2)	42(87.5)	**0.033**	27(79.4)	28(82.4)	0.758
Laparoscopic surgery, n (%)	7(12.3)	10(20.8)	0.236	2(5.9)	9(26.5)	**0.045**
Operation time, median (IQR), min	180(160-200)	185(155-230)	0.105	180(160-200)	195(160-230)	0.058
Blood loss, median (IQR), ml	250(200-350)	300(200-475)	0.327	300(200-500)	300(200-450)	0.561
Blood transfusion, n (%)	6(10.5)	3(6.3)	0.504	4(11.8)	3(8.8)	1.000
Positive margin, n (%)	5(8.8)	2(2.1)	0.450	2(5.9)	2(5.9)	1.000
Differentiation, well/moderate: poor	45:12	39:9	0.811	28:6	27:7	0.758
Vascular invasion, n (%)	12(21.1)	7(14.6)	0.391	7(20.6)	7(20.6)	1.000
Lymph node metastasis, n (%)	5(8.8)	3(6.3)	0.724	4(11.8)	1(2.9)	0.356
8thAJCC TNM staging, I: II: III	32:20:5	34:11:3	0.298	33:19:5	34:11:3	0.389

PSM, propensity score matching; NAR, non-anatomical resection; AR, anatomical resection; IQR, interquartile range; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; ALT, alanine transaminase; TBIL, total bilirubin; ALB albumin, PT, prothrombin time; WBC, white blood cell; HB, hemoglobin; PLT, platelet.
Bold values: statistically significant P values.

hemihepatectomy (n=11); sectionectomy (n=9); segmentectomy (n=16); combined resection of segments (n=10).

Postoperative outcomes

The overall incidence rates of postoperative complications and 30-day mortality were 34.3% (43/105) and 1% (1/105), respectively. The lengths of postoperative hospital stays and incidence rates of complications were similar between the two matched groups (Table 2). None of the patients experienced intraperitoneal bleeding within 72 hours after surgery. In the NAR group, one patient developed bile leakage after hepatectomy and underwent percutaneous catheter drainage for two months. One patient in each group developed postoperative hepatic failure; after conservative treatment, the AR patient recovered, whereas the NAR patient died 25 days after surgery. Postoperative infection (definite positive after bacterial culture) occurred in three patients in each group; however, these patients recovered after treatment with antibiotics and immune regulation. Other common complications included pleural effusion and ascites, which occurred at similar rates between both groups and required ultrasound-guided percutaneous drainage. There were no significant differences between the two groups in the severity of complications according to the Clavien–Dindo classification.

Long-term survival

A total of 105 patients were followed up for various periods (range=0.8–97 months; median=42 months). The 1-year, 3-year, and 5-year OS rates for all patients were 88.6%, 59.8%, and 29.0%, respectively. Correspondingly, the 1-year, 3-year, and 5-year RFS rates for all patients were 75.2%, 42.9%, and 22.8%, respectively. The 1-year, 3-year, and 5-year OS rates were significantly higher in the AR group as compared to those in the NAR group (91.7% vs 86.0%; 70.0% vs 51.1%; 36.8% vs 22.3%, respectively; *P*=0.002; Figure 2A). The 1-year, 3-year, and 5-year RFS rates were also higher in the AR group as compared to those in the NAR group (79.2% vs 71.9%; 56.0% vs 31.0%; 32.6% vs 14.4%, respectively; *P*=0.002; Figure 2B). Tables 3, 4 show the results of the stratified analyses (Cox proportional hazard regression analysis and log-rank test) for the predictors of RFS and OS rates. Univariate analyses revealed that the presence of HBsAg (positive vs negative) and cirrhosis (yes vs no), tumor nodularity (multiple vs solitary), tumor size (>5 cm vs ≤5 cm), resection type (AR vs NAR), surgical margin (R1 vs R0), differentiation (poor vs moderate/well), and the presence of lymph node metastasis and vascular invasion (yes vs no) were prognostic factors for RFS. Multivariate analyses revealed that the presence of: multiple tumors (hazard ratio [*HR*]=2.560, 95% confidence interval [*CI*]=1.346–4.868, *P*=0.004), larger tumors (>5 cm) (*HR*=2.036, 95% *CI*=1.174–3.534, *P*=0.011), AR (*HR*=0.573, 95% *CI*=0.334–0.982, *P*=0.043), lymph node metastasis (*HR*=3.043, 95% *CI*=1.348-6.869, *P*=0.007), and vascular invasion (*HR*=2.325, 95% *CI*=1.220–4.432, *P*=0.010) were significant predictors of RFS. Similarly, univariate analyses found that the presence of cirrhosis (yes vs no), tumor nodularity (multiple vs solitary), tumor size (>5 cm vs ≤5 cm), resection type (AR vs NAR), surgical margin (R1 vs R0), and the presence of lymph node metastasis and vascular invasion (yes vs no) were prognostic factors for OS. Multivariate analysis revealed that cirrhosis (*HR*=1.921, 95% *CI*=1.101–3.352, *P*=0.022), the presence of larger tumors (>5 cm) (*HR*=1.793, 95% *CI*=1.015–3.165, *P*=0.044), AR (*HR*=0.548, 95% *CI*=0.316–0.950, *P*=0.032), the presence of lymph node metastasis (*HR*=3.108, 95% *CI*=1.429–6.761, *P*=0.004), and vascular invasion (*HR*=3.544, 95% *CI*=1.831–6.862, *P*=0.001) were significant predictors of OS.

TABLE 2 Comparison of postoperative outcomes.

Postoperative outcomes	NAR(n=57)	AR(n=48)	*P* value
	n (%)	n (%)	
30-day mortality	1(2.9)	0(0)	1.000
Postoperative hospital stay (days)	13(9-16)	12(8-17)	0.813
Overall complication	15(26.3)	11(22.9)	0.688
Infection	3(5.3)	3(6.3)	1.000
Bile leakage	1(1.8)	0(0)	1.000
Pleural effusion	5(8.7)	3(6.3)	0.724
Postoperative ascites	5(8.8)	4(8.3)	1.000
Liver failure	1(1.8)	1(2.1)	1.000
Severity of complication (Clavien–Dindo)			
Grade I-II	9(26.5)	8(23.5)	0.779
Grade III-IV	1(2.9)	1(2.9)	1.000

NAR, non-anatomical resection; AR, anatomical resection.

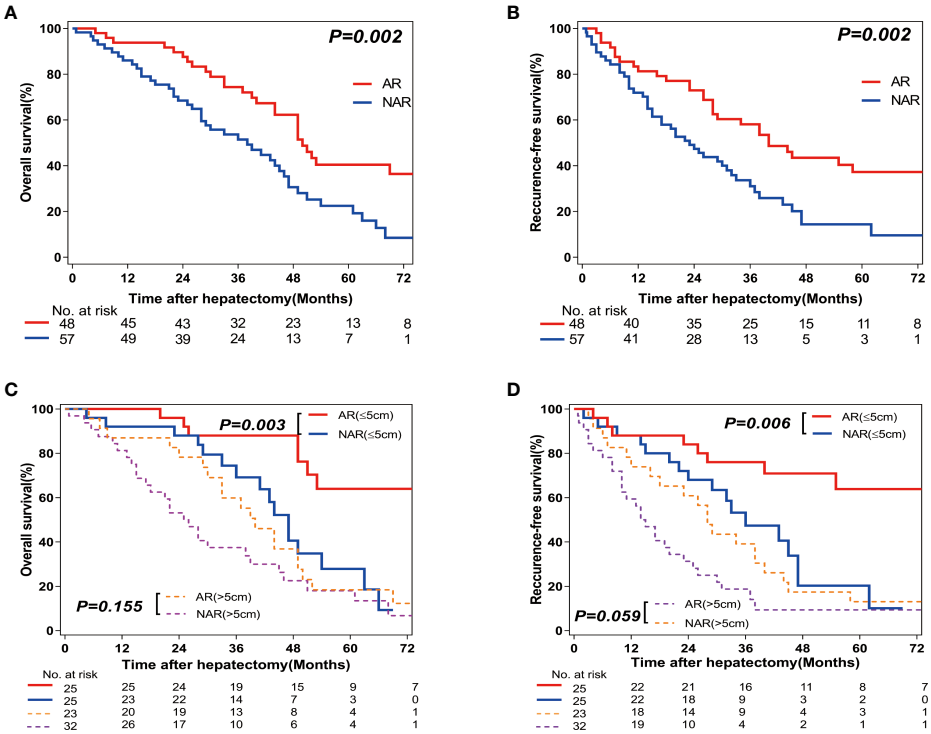

FIGURE 2
Overall survival (OS) and Recurrence-free survival (RFS) rates after Anatomic resection (AR) versus Non-anatomic resection (NAR) for combined hepatocellular-cholangiocarcinoma (cHCC-CCA) patients. **(A)** Overall survival (OS) and **(B)** recurrence-free survival (RFS) curves of cHCC-CCA patients in AR (n=57; *P*=0.002) and NAR (n=48; *P*=0.002) groups. **(C)** Overall survival (OS) and **(D)** recurrence-free survival (RFS) curves of cHCC-CCA patients with tumors ≤5 cm in size (n=50, *P*=0.006 and *P*=0.003, respectively) and >5 cm in size (n=55, *P*=0.059 and *P*=0.155, respectively).

Since tumor size may be associated with prognosis, the patients were further classified into subsets according to tumor size: tumor size <5 cm (n=50) and >5 cm (n=55). In the patients with smaller tumors (<5 cm), higher RFS and OS rates were observed in the AR (n=25) group as compared with those in the NAR (n=25) group (*P*=0.006 and *P*=0.003, respectively; Figures 2C, D). In the patients with larger tumors (>5 cm), there were no differences in RFS and OS rates between the AR (n=23) and NAR (n=32) groups (*P*=0.059 and *P*=0.155, respectively; Figures 2C, D).

Patient characteristics and long-term outcomes after PSM

After the 1:1 PSM, 68 patients were identified and classified into propensity-matched anatomical resection (PSM-AR) (n=34) and propensity-matched non-anatomical resection (PSM-NAR) groups (n=34) (Table 1). Except for the high laparoscopic resection rate in the PSM-AR group (26.5% vs 5.9%; *P*=0.045), there were no significant differences in demographic and clinicopathologic characteristics between the two groups after matching (Table 1). The operation time tended to be shorter in PSM-NAR (median time=180 in the PASM-NAR group as compared to 195 minutes for the PSM-NAR group; *P*=0.058).

Among the 68 patients included in this analysis, the 1-year, 3-year, and 5-year OS rates were higher in the PSM-AR group as compared to those in the PSM-NAR group (94.1% vs 88.2%; 65.9% vs 41.2%; 31.7% vs 14.0%, respectively; *P*=0.002; Figure 3A). The 1-year, 3-year, and 5-year RFS rates were also higher in the PSM-AR group as compared to those in the PSM-NAR group (79.4% vs 67.6%; 49.6% vs 32.4%; 30.2% vs 13.2%, respectively; *P*=0.010; Figure 3B).

Discussion

The clinical significance of choosing AR or NAR in treating cHCC-CCA remains unclear because of the relative rarity of this primary liver malignancy, which has an incidence of 1.8% (118/6552; as observed in our study, which is consistent with previous reports) (6). In this single-center study, we have demonstrated that cHCC-CCA patients who underwent AR surgeries had

TABLE 3 Univariate and multivariate analyses of prognostic factors of recurrence-free survival.

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (≥60 vs <60years)	1.636 (0.967–2.766)	0.066		
Sex (female vs male)	0.812 (0.416–1.586)	0.543		
ECOG-PS (1 vs 0)	1.225 (0.719–2.089)	0.455		
HBsAg (positive vs negative)	1.661 (1.021–2.700)	**0.041**	1.368 (0.780–2.399)	0.275
AFP (>20 vs ≤20ng/ml)	1.088 (0.650–1.821)	0.749		
CEA (>5 vs ≤5ng/ml)	1.312 (0.742–2.320)	0.350		
CA199 (>37 vs ≤37U/L)	1.131 (0.714–1.791)	0.600		
Splenomegaly (yes vs no)	2.138 (1.297–3.523)	**0.003**	1.222 (0.652–2.288)	0.531
Child Pugh (B vs A)	0.514 (0.162–1.636)	0.260		
Tumor nodularity (multiple vs solitary)	5.132 (2.910–9.050)	**<0.001**	2.560 (1.346–4.868)	**0.004**
Tumor size (>5 vs ≤5cm)	2.852 (1.748–4.652)	**<0.001**	2.036 (1.174–3.534)	**0.011**
Procedure (laparoscopic vs. open)	0.834 (0.426–1.633)	0.596		
Resection (AR vs NAR)	0.475 (0.294–0.769)	**0.002**	0.573 (0.334–0.982)	**0.043**
Operation time (>180 vs ≤180mins)	0.881 (0.553–1.405)	0.596		
Blood loss (>500 vs ≤500ml)	0.681 (0.326–1.419)	0.305		
Transfusion (yes vs no)	0.657 (0.264–1.635)	0.367		
Surgical margin (R1 VS R0)	2.955 (1.255–6.958)	**0.013**	1.561 (0.581–4.195)	0.377
Differentiation (poor vs moderate/well)	1.762 (1.022–3.038)	**0.042**	1.236 (0.671–2.277)	0.496
Lymph node metastasis (yes vs no)	2.882 (1.354–6.133)	**0.006**	3.043 (1.348–6.869)	**0.007**
Vascular invasion (yes vs no)	3.661 (2.104–6.370)	**<0.001**	2.325 (1.220–4.432)	**0.010**

HR, hazards ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; AR, anatomical resection; NAR, non-anatomical resection.
Bold values: statistically significant P values.

longer DFS and OS times than those who underwent NAR surgeries, (both, before and after PSM analysis), especially for tumors <5 cm in diameter. To the best of our knowledge, this is the first report that compares the surgical outcomes of AR versus NAR in the treatment of cHCC-CCA; we find that patients who underwent AR, had better surgical outcomes than those who underwent NAR.

Although cHCC-CCA has features of both HCC and CC, several studies have observed that cHCC-CCA shares more etiological features with HCC than with iCCA, especially with respect to its epithelial characteristics (5, 15). In our study, the clinicopathological features of cHCC-CCA were more similar to those of patients suffering from HCC infected with HBV (hepatitis B virus), both of which are associated with elevated AFP levels in most patients. The results of this study are consistent with those of previous studies (15, 21). In clinical settings, cHCC-CCA is often misdiagnosed as either HCC or iCCA *via* imaging or hematology tests due to non-specific clinical manifestations, and a confirmed diagnosis of cHCC-CCA usually requires surgical resection (22). Since preoperative biopsy is not routinely used to diagnose cHCC-CCA (as large sampling areas are required and have low sensitivity of detection), some studies have explored the use of other risk factors to differentiate between cHCC-CCA and HCC or iCCA. Some of these factors include sex (men are more likely to develop cHCC-CCA than women), and the presence of chronic liver damage, cirrhosis, hepatitis infection, familial history of liver cancer, alcoholism, and diabetes (21, 23). Although both CA199 and AFP levels are expected to be higher than normal in cHCC-CCA patients, in this study, we found that elevated AFP levels were more common than elevated CA199 levels. Furthermore, 85.7% of cHCC-CCA patients in our study were men and 62.9% of them had HBV infections, which is consistent with previous reports (23, 24). Our results indicate that the clinicopathological characteristics of cHCC-CCA in the patients included in our study resemble those of HCC more than iCCA.

Surgical resection is widely accepted as an optimal curative treatment for cHCC-CCA and can provide patients with a chance of long-term survival (13, 25).The main objectives of surgical resectioning in treating cHCC-CCA are to completely remove the tumor, preserve sufficient residual liver volume for survival, and ensure negative resection margins. Unfortunately, until now, the prognostic differences in treating cHCC-CCA with either AR or NAR surgeries have not been reported. Usually, treatment with AR reduces tumor recurrence as it involves the removal of tumor-bearing portal vein branches and corresponding liver parenchyma. Since this supports long-term survival, several studies have reported that AR is superior

TABLE 4 Univariate and multivariate analyses of prognostic factors of overall survival.

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (≥60 vs <60years)	1.301 (0.741–2.281)	0.359		
Sex (female vs male)	0.735 (0.364–1.487)	0.392		
ECOG-PS (1 vs 0)	1.082 (0.625–1.875)	0.778		
HBsAg (positive vs negative)	1.389 (0.849–2.274)	0.191		
AFP (>20 vs ≤20ng/ml)	1.327 (0.774–2.275)	0.304		
CEA (>5 vs ≤5ng/ml)	1.397 (0.776–2.514)	0.265		
CA199 (>37 vs ≤37U/L)	1.117 (0.696–1.793)	0.646		
Splenomegaly (yes vs no)	2.581 (1.552–4.294)	**<0.001**	1.921 (1.101–3.352)	**0.022**
Child Pugh (B vs A)	0.623 (0.196–1.984)	0.424		
Tumor nodularity (multiple vs solitary)	3.079 (1.886–5.164)	**<0.001**	1.515 (0.814–2.817)	0.190
Tumor size (>5 vs ≤5cm)	2.728 (1.650–4.510)	**<0.001**	1.793 (1.015–3.165)	**0.044**
Procedure (laparoscopic vs. open)	1.157 (0.586–2.283)	0.675		
Resection (AR vs NAR)	0.465 (0.284–0.761)	**0.002**	0.548 (0.316–0.950)	**0.032**
Operation time (>180 vs ≤180mins)	1.024 (0.635–1.653)	0.922		
Blood loss (>500 vs ≤500ml)	0.806 (0.385–1.688)	0.567		
Transfusion (yes vs no)	0.620 (0.249–1.544)	0.305		
Surgical margin (R1 VS R0)	3.736 (1.551–8.997)	**0.003**	2.024 (0.762–5.376)	0.157
Differentiation (poor vs moderate/well)	1.556 (0.895–2.703)	0.117		
Lymph node metastasis (yes vs no)	2.424 (1.149–5.112)	**0.020**	3.108 (1.429–6.761)	**0.004**
Vascular invasion (yes vs no)	4.103 (2.307–7.297)	**<0.001**	3.544 (1.831–6.862)	**<0.001**

HR, hazards ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; AR, anatomical resection; NAR, non-anatomical resection.
Bold values: statistically significant P values.

to NAR for the treatment of HCC or iCCA with resection (17, 26, 27). NAR is considered to be beneficial for patients with cirrhosis or poorly preserved liver function (28). Since cHCC-CCA resembles both, HCC and iCCA, the long-term outcomes of surgical resection may be similar to those of HCC and iCCA; however, it is important to have data-backed proof of differences in surgical outcomes of cHCC-CCA patients after AR or NAR surgeries. Although there were no significant differences in the occurrences or types of postoperative complications between the two surgical methods, we found that AR is prognostically

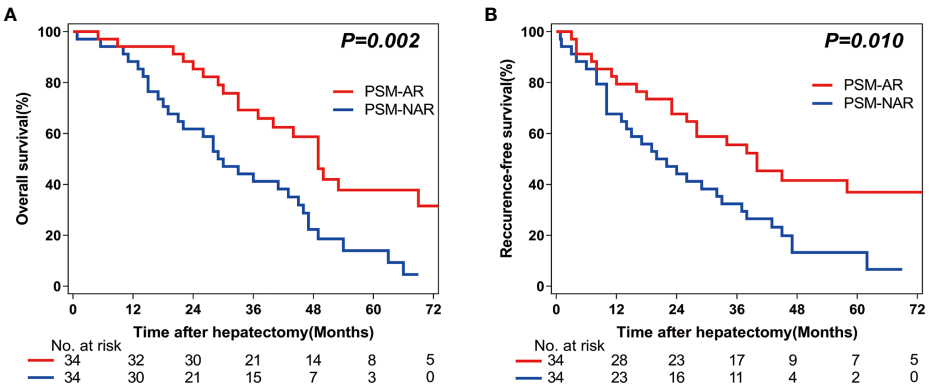

FIGURE 3
Overall survival (OS) and Recurrence-free survival (RFS) rates after Anatomic (AR) versus Non-anatomic resection (NAR) for combined hepatocellular-cholangiocarcinoma (cHCC-CCA) patients after propensity score matching (PSM). **(A)** Overall survival (OS) and **(B)** recurrence-free survival (RFS) curves of cHCC-CCA patients in PSM-AR (n = 34) and PSM-NAR (n = 34) groups after propensity score matching (PSM) (*P* = 0.002, P = 0.010, respectively).

superior to NAR for cHCC-CCA treatment. Our results (both, before and after PSM) show that AR significantly improved the RFS and OS times for cHCC-CCA patients.

Multivariate analyses also showed that tumor size and nodularity, as well as the presence of lymph node metastasis and vascular invasion were independent risk factors for postoperative survival of cHCC-CCA patients; these patterns are consistent with those for patients with HCC or iCCA (29–33). Tumor size may influence surgical outcomes for HCC patients (34); this was shown in a large-scale study from Japan, which found that the recurrence rates for HCC patients with tumors of diameter 2–5 cm were significantly lower for those who underwent AR surgery rather than for those who underwent NAR surgery. However, there were no significant differences in surgical outcomes after liver resection for HCC tumors ≤2 cm or ≥5 cm in size between the AR and NAR groups (35). Due to the similarities between HCC and cHCC-CCA, tumor size can be expected to be a crucial risk factor for surgical outcomes of AR or NAR surgeries in cHCC-CCA patients. In this study, stratified analysis showed that AR provides a better long-term survival benefit than NAR for patients with tumors ≤5 cm in size. However, there were no significant differences in RFS and OS at 1, 3, and 5 years after resection surgery for patients with tumors >5 cm in size. One reason for this inconsistency could be that the cHCC-CCA tumors in the patients included in this study were more similar to CCA tumors than to HCC tumors; for CCA tumors, AR surgery provides no extra survival benefits over NAR surgery. Furthermore, the diameters of all the tumor masses in this study were >2.2 cm. Our results, therefore, suggest that AR should be recommended for cHCC-CCA patients with small tumors.

Despite our clear-cut results, this study has several limitations. Of these, one is that this study has a small sample size with all samples drawn from a single center. Second, this is a retrospective study, which means that there is a high chance of it having selection biases despite our use of PSM analysis. Third, we have not analyzed the impact of postoperative therapy on the long-term outcomes in patients due to unavailable data. In addition, not all patients included in this study underwent lymph node dissection, as several had normal lymph nodes (as observed by preoperative imaging). We recommend that more prospective studies with larger sample sizes and RCT studies be performed to fully evaluate the relative merits of AR and NAR surgeries in treating cHCC-CCA.

Conclusion

In conclusion, the clinicopathologic characteristics of cHCC-CCA usually resemble those of HCC more than those of iCCA. Irrespective of the application of PSM, we found that AR was associated with better surgical outcomes as compared to NAR for patients with cHCC-CCA, especially for tumors of size ≤5 cm in diameter.

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.

Author contributions

Conception and design, W-QW, E-LZ, and S-HY. Analysis and interpretation of data, all authors. Drafting the article or revising it critically for important intellectual content, all authors. Final approval of manuscript, all authors. 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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Case Report: Combining liver partition and portal vein ligation after thrombectomy for tumor isolation (CLAPT) to treat advanced hepatocellular carcinoma with portal vein tumor thrombosis

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Background: Primary liver cancer is the third leading cause of cancer-related deaths worldwide in 2020, and hepatocellular carcinoma (HCC) is the major pathological type. Patients with HCC complicated with portal vein tumor thrombosis (PVTT) have a poor prognosis, and controversies regarding treatment options exist among international scholars. Patients with VP4 or Cheng's type III classification are generally considered ineligible for surgical treatment.
Methods: We retrospectively analyzed three cases of HCC with PVTT who underwent a novel modified surgical procedure. The procedure included portal vein thrombectomy and portal vein ligation with liver parenchymal separation for the resection of the tumor thrombus involving the main portal vein trunk and for the isolation of the giant tumor. The three cases were then treated with targeted drugs postoperatively.
Results: One case developed acute renal failure in the perioperative period, and the renal function gradually recovered after the treatment. The two remaining cases recovered uneventfully postoperatively. The prognosis of the three patients was encouraging. Only one patient died of lung metastasis after 13 months, and the remaining patients were still alive after 41 and 21 months, respectively.
Conclusions: We provide a new possible surgical option for patients with advanced HCC with PVTT. The surgical procedure was inspired by associating liver partition with portal vein ligation for staged hepatectomy and portal vein thrombectomy. The survival time was significantly prolonged after the patients underwent thrombectomy, tumor isolation, and postoperative nonsurgical treatment. Hence, the combination of liver partition and portal vein ligation after thrombectomy for tumor isolation has the potential for the treatment of advanced HCC with PVTT.

KEYWORDS

hepatocellular carcinoma, portal vein tumor thrombosis, combining liver partition and portal vein ligation after thrombectomy for tumor isolation, associating liver partition and portal vein ligation for staged hepatectomy, future liver remnant

Introduction

Primary liver cancer is a common malignant tumor and has the third highest mortality rate among global malignant tumor-related diseases. Hepatocellular carcinoma (HCC) is the major pathological type (1). Most patients with HCC have reached the advanced stage after their initial diagnosis and have missed the optimal treatment time. Only about 30% of patients with HCC can receive surgery (2). HCC cells invade the portal vein system and form portal vein tumor thrombosis (PVTT) due to the anatomical characteristics of the liver blood supply system and the biological characteristics of liver cancer cells. The prognosis of patients with HCC and PVTT is generally poor, and the average median survival time is only 2.7 months (3). Surgery is the first-line treatment for HCC, but international scholars have different viewpoints regarding the suitable surgical treatment for patients with HCC combined with PVTT. The American Association for the Study of Liver Diseases (AASLD) guidelines and the Barcelona Clinic for Liver Cancer (BCLC) staging system recommend sorafenib as a standard therapy for patients suffering from HCC with PVTT (4); however, the prognosis remains poor, and the median survival is only 8.1 months (5). Compared with the conservative opinions of European and American guidelines, Asian scholars support the use of more active surgical intervention strategies (6). Associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) is a new surgical operation for patients with insufficient future liver remnant (FLR) (7). ALPPS can stimulate the rapid proliferation of the remaining liver in a short period of time by changing the liver hemodynamics and *in situ* separation, leading to the safe resection of liver tumors. Therefore, ALPPS is a promising surgical treatment for HCC combined with PVTT and can bring new hope for patients while avoiding postoperative liver failure (8). Even if patients cannot undergo secondary surgery due to poor FLR hyperplasia or other reasons, the tumor isolation effect brought about by this surgery coupled with transcatheter arterial chemoembolization (TACE), tumor-targeted drugs, and other comprehensive treatment methods make the entire approach feasible (9).

We developed ALPPS, a novel modified surgical operation, by combining liver partition and portal vein ligation after thrombectomy for tumor isolation (CLAPT). The process can split the tumor by removing portal vein thrombi combined with portal vein branch ligation and liver parenchymal separation. In this study, we reported three cases of HCC combined with PVTT that were unable to undergo one-step hepatectomy due to insufficient FLR assessment but were successfully subjected to CLAPT. We described the main points of the modified technique and analyzed its feasibility, safety, and effectiveness.

Materials and methods

Patient base condition and preoperative evaluation

Case 1 is a 61-year-old male. His alpha fetoprotein (AFP) level was more than 20,000 μg/L, and his liver function was Class A according to the Child–Pugh classification. The preoperative indocyanine green (ICG) retention 15 was 7.6%, and the FibroScan liver stiffness value was 18.3 kPa (liver elastomeric techniques). The preoperative image of the enhanced CT scan showed that the right lobe of the liver had a large, slightly low-density 10.7 cm × 10.6 cm shadow and that the main stem and right branch of the portal vein were filling defects. The tumor was mainly located in segments 6, 7, and 8 (**Figures 1A–C**). No extrahepatic metastases were found in other auxiliary examinations. The main preliminary diagnosis was as follows: massive HCC with right portal vein (RPV) tumor thrombus (Cheng's type III or VP4).

Case 2 is a 35-year-old male. His AFP level was 254 μg/L, and the liver function was Class A. The preoperative ICG retention 15 was 4.5%, and the FibroScan liver stiffness value was 20.6 kPa. The preoperative enhanced CT imaging of the upper abdomen showed a huge mass (12.7 cm × 11.6 cm) of each segment of the right liver, a filling defect from the right branch of the portal vein to the main trunk, and a small tumor in s4 (**Figures 1D–F**). No extrahepatic metastasis was found. The preliminary diagnosis included the following: massive HCC with right portal vein tumor thrombus (Cheng's type III or VP4).

Case 3 is a 45-year-old man who had normal AFP and Child–Pugh Class A of liver function. The preoperative ICG retention 15 was 9.6%, and the FibroScan liver stiffness value was 16.5 kPa. The enhanced CT scans suggested the following: diffuse right liver cancer with tumor thrombus formation in the main portal vein (MPV) and left and right branches; the tumor was mainly located in the right lobe and had a maximum size of 8.8 cm; and liver cirrhosis with portal hypertension (**Figures 1G–I**). Extrahepatic metastasis was not observed. The preliminary diagnosis included the following: multiple liver tumors with portal vein tumor thrombosis (Cheng's type III or VP4).

The basic clinical data of the three cases are shown in **Table 1**. Patients with cirrhosis without portal hypertension usually require an FLR of at least 40% to minimize the occurrence of postoperative liver failure (10). Based on the CT examination, the standard liver volume (SLV) of the three cases and the proportion of the FLR were calculated using the West China formula and the IQQA-Liver system, respectively (11, 12). The results are shown in **Table 1**. The FLR of the three cases were obviously insufficient to complete a one-step

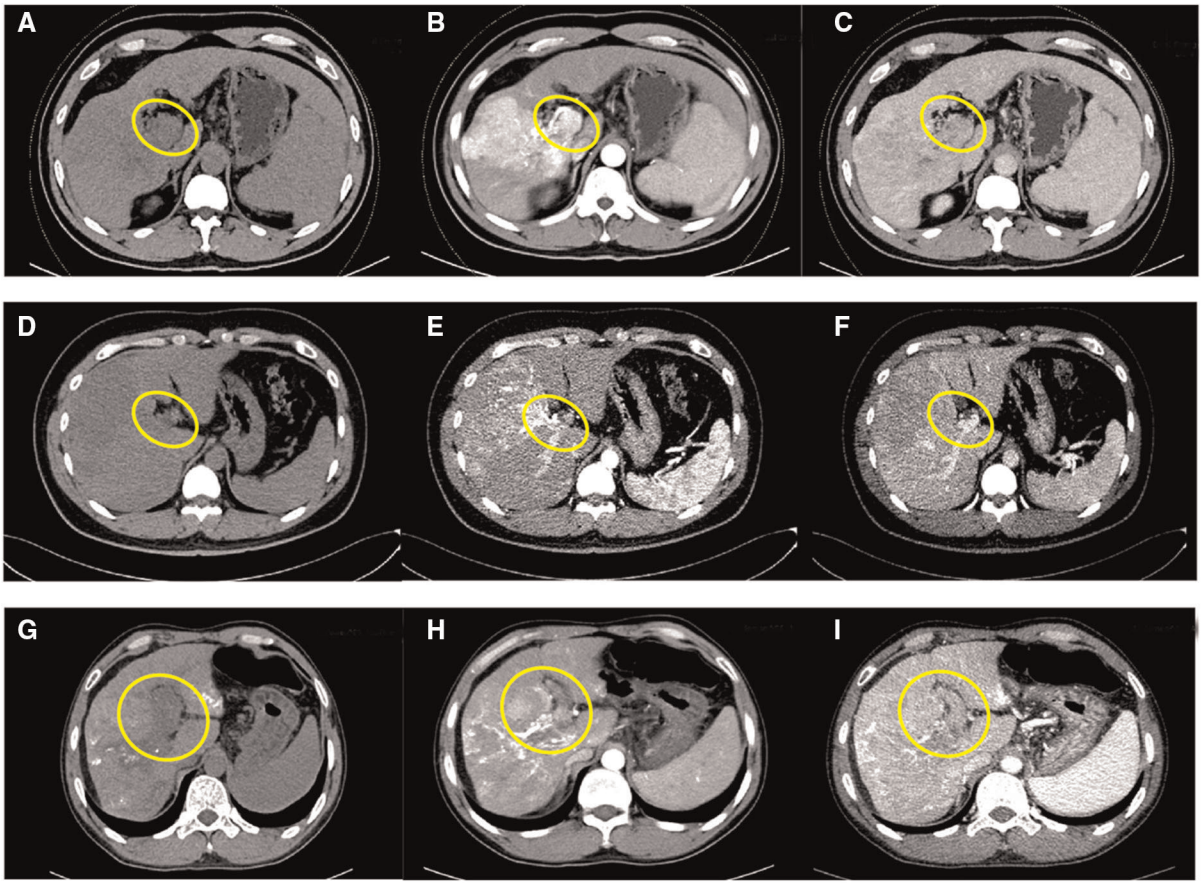

FIGURE 1
Preoperative CT images of case 1: unenhanced phase (A), arterial phase (B), and venous phase (C); preoperative CT images of case 2: unenhanced phase (D), arterial phase (E), and venous phase (F); preoperative CT images of case 3: unenhanced phase (G), arterial phase (H), and venous phase (I); inside the yellow circle is the portal vein tumor thrombus.

TABLE 1 Clinical information of the three cases.

Patient No.	Age	Gender	HBV	AFP (μg/L)	Max Tumor Size (cm)	BCLC	Child–Pugh	MELD	PVTT classification	ICG R15 (%)	FibroScan (kp)	SLV (ml)	TLV (ml)	FLR (ml)	FLR/SLV (%)
Case1	61	Male	+	>200,000	10.7	C	A	7	Cheng's type III or VP4	7.6	18.3	1,365.52	2,063.43	471.65	34.54%
Case2	35	Male	+	254	12.7	C	A	5	Cheng's type III or VP4	4.5	20.6	1,358.23	1,995.18	315.78	23.25%
Case3	45	Male	+	2.76	8.8	C	A	8	Cheng's type III or VP4	9.6	16.5	1,239.84	1,883.21	465.18	37.52%

HBV, Hepatitis B virus; AFP, alpha fetoprotein; BCLC, Barcelona Clinic for Liver Cancer; MELD, model for end-stage liver disease; PVTT, portal vein tumor thrombus; ICG R15, indocyanine green retention rate at 15 min; SLV, standard liver volume; TLV, total liver volume; FLR, future liver remnant.

liver tumor resection and portal vein thrombectomy, so we implemented CLAPT. This study was approved by the hospital ethical review committee, and all patients signed an informed consent form in accordance with medical ethics.

Surgical procedure

Three patients were under general anesthesia when subjected to CLAPT. The patient was placed in the supine

position. The surgical entry into the abdomen was layer-by-layer through the reverse "L" incision. The first hepatic portal was exposed, and the hepatic portal lymph node was cleared. The RPV distant to the bifurcation, the left portal vein (LPV), and the MPV located distal to the PVTT were occluded by vascular clip (Figure 2G). A small incision of about 1 cm was opened in the RPV or MPV. Oval forceps and thrombus removal catheter were used to remove the tumor thrombus. The PVTT in the RPV or MPV was then removed from the opening, and the possible residual tumor thrombus was flushed with portal blood flow by releasing the vaso-occlusive band of the MPV (Figure 2H). The MPV was occluded, and the residual tumor thrombus was flushed with retrograde blood by releasing the vascular occlusion band of the LPV. The portal vein cavity was flushed with heparin saline. If the tumor thrombus is tightly attached to the blood vessel wall and is difficult to peel, then the blood vessel segment can be resected, and artificial blood vessel reconstruction can be performed. After confirming that no residual tumor thrombus was present, the stump was closed by a 5-0 hemo-seal prolene. The right branch of the portal vein was disconnected, and the broken end was ligated (Figures 2I,J). After ligating the right branch of the portal vein, the left and right hepatic ischemia lines became visible. A harmonic scalpel and a cavitron ultrasonic surgical aspirator were used to split the liver parenchyma along the hepatic ischemia line, leaving the middle hepatic vein on the liver side of the tumor. The liver was split into the root of the proximal middle hepatic vein and in front of the inferior vena cava (Figure 2K). After checking the liver wound and ensuring the absence of bleeding or bile leakage, the free omentum was cropped to cover the wound. A drainage tube was then placed in the liver section and under the right diaphragm. During the operation, tumor puncture was performed to clarify the pathological results of the patients. A brief operation diagram is shown in Figures 2A–F. Postoperative monitoring of vital signs, blood routine, liver function, coagulation function, and other inspection indicators was conducted. CT and ultrasound scanning was also performed.

Results

Intraoperative and postoperative conditions

Based on intraoperative exploration, the liver of case 1 showed chronic liver disease and cirrhosis. The main tumor was located in the right liver, and multiple subfocals were seen around it. The right branch of the portal vein thickened, and tumor thrombi adhered to the wall and protruded to the main portal vein. Tumor thrombi were also formed on the right branch of the portal vein. For case 2, the liver had chronic liver disease and cirrhosis, and a huge mass was seen in the right lobe. Cancer thrombi adhered to the wall, from the right branch of the portal vein to the main stem. The liver of case 3 showed chronic liver disease and cirrhosis. The tumor was found in the right lobe of the liver, with subfocuses in the S3 and S4 segments. The main portal vein, the left branch, and the right branch were filled with tumor thrombi (Table 2). All three patients had normal postoperative vital signs. The patients were instructed to get out of bed 1–2 days after the surgery and have liquid food after anal exhaust. The results of blood routine, liver function, and blood coagulation function tests were rechecked after the operation (Table 3). In case 1, the number of white blood cells continued to increase after the surgery. Oliguria occurred on the fifth day after the surgery, and the continuous increase in serum creatinine was monitored. In acute kidney injury, the renal function gradually recovered after the continuous renal replacement therapy. The postoperative liver failure was graded as B, and the Clavien–Dindo classification was grade III. The postoperative levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased. The abdominal drainage of POD7 reached 1,200 ml per day and improved after liver protection, diuresis, and albumin infusion. Cases 2 and 3 showed a transient increase in the ALT and AST levels after the operation; however, the levels gradually returned to normal after liver protection treatment. The postoperative liver failure was grade A, and the Clavien–Dindo complications were all grade I. The three patients underwent CT examination 2 weeks after the operation, and the FLR showed different degrees of regeneration. According to the IQQA system, the FLR of the three patients was calculated, and the SLV was determined. From case 1 to case 3, the FLR/SLV of the three patients were 53.82%, 36.36%, and 49.87%, respectively. The tumors of the three cases showed necrosis and atrophy due to the ligation of the lateral portal vein branches. Although FLR in cases 1 and 3 seemed to meet the criteria for resectability at 2 weeks after surgery, we suggest that patients should choose targeted agents along with TACE treatment considering that the patients are at an advanced stage for tumor subtyping.

Pathology and follow-up

The pathology report for case 1 included the following: low to moderately differentiated HCC and Edmondson–Steiner grade III; and Ishak scores of peripheral liver tissue, with 6 points for inflammation and 6 points for fibrosis. The pathology report for case 2 was as follows: moderately differentiated HCC and Edmondson–Steiner grade III; and Ishak scores of 9 points for inflammation and 6 points for fibrosis. The pathology report for case 3 comprised the following: moderately differentiated HCC and Edmondson–

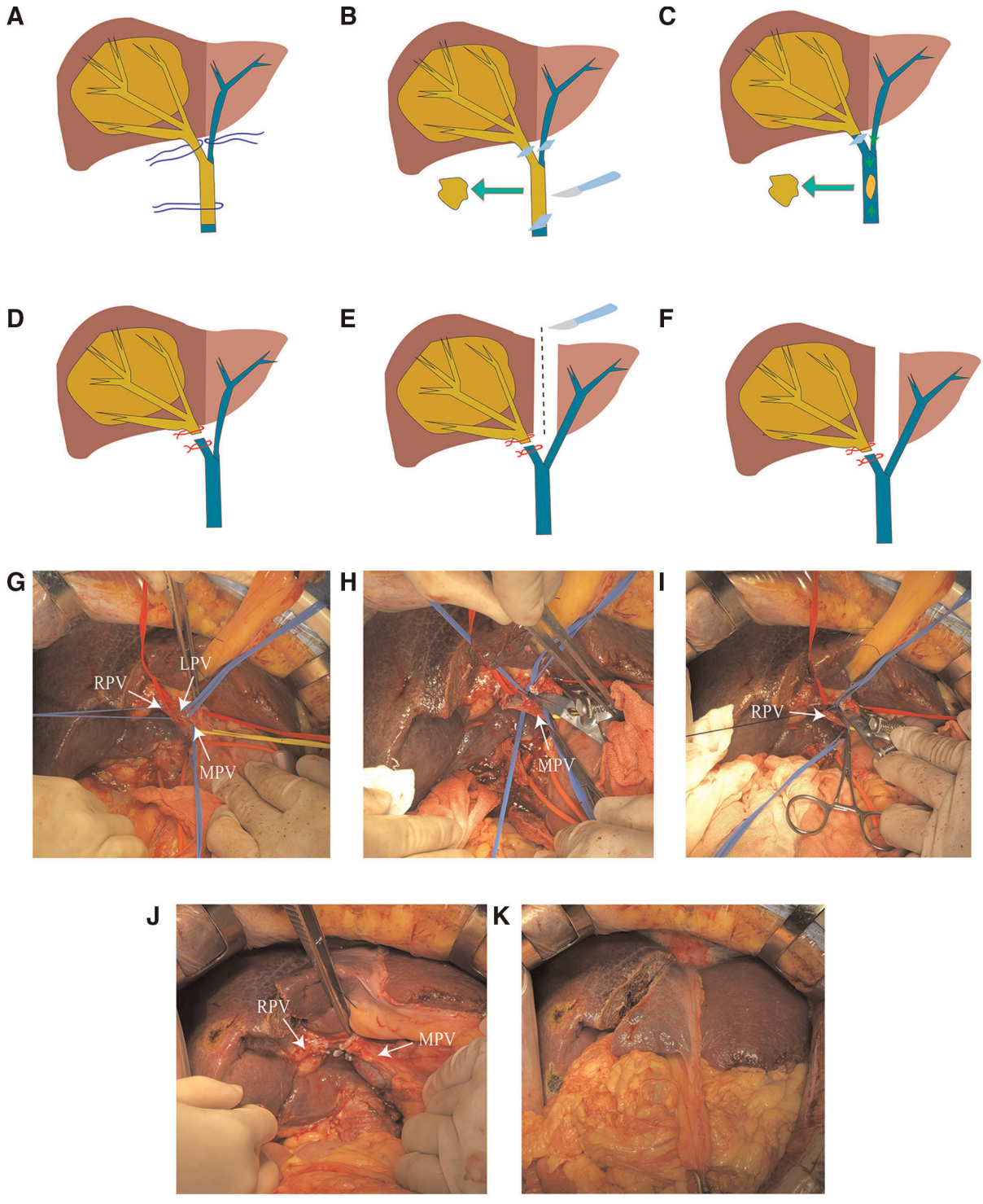

FIGURE 2
(**A**) Anatomical separation showing the LPV, RPV, and MPV. (**B**) Blocking the blood flow of the LPV, RPV, and PV and removing the tumor thrombus in the portal vein (PVTT). (**C**) Flushing out possible residual tumor thrombi by releasing MPV blood flow. (**D**) Ligation of the right portal vein stump. (**E**) Separation of the left and right liver parenchyma. (**F**) Completion of the CLAPT procedure. (**G**) Anatomical separation showing the LPV, RPV, and MPV. (**H**) Cutting the portal vein to remove the tumor thrombus. (**I**) Ligation of the RPV stump. (**J**) Separation of the left and right liver parenchyma. (**K**) Photograph of the operation completed.

TABLE 2 The three cases of intraoperative characteristics, postoperative pathological results and follow-up results.

Patient No.	Operation time (minute)	Bleeding volume (ml)	Intraoperative urine output (ml)	Pathological type	inflammation	fibrosis	Post-op treatment	tumor metastasis	Survival time (month)
Case1	390	400	1,300	Low–moderately differentiated HCC	6	6	No	No	41 (still alive)
Case2	355	100	1,550	Moderately differentiated HCC	9	6	TACE (once)	lung	13 (dead)
Case3	380	200	900	Moderately differentiated HCC	9	6	TACE (once)	no	21 (still alive)

TACE, Transcatheter arterial chemoembolization.

TABLE 3 Clinical characteristics of the three cases about preoperative and postoperative.

Patient	Time	WBC ($\times10^9$/L)	PLT ($\times10^9$/L)	ALT (U/L)	AST (U/L)	TBIL (μmol/L)	INR	Abdominal drainage (ml)
Case 1	Preoperative	7.65	284	46	65	7.1	1.05	NA
	POD 1	12.49	261	567	618	10.6	1.20	12
	POD 3	15.16	223	678	338	21.5	1.22	20
	POD 5	17.11	208	261	108	9.8	1.21	850
	POD7	20.23	213	116	92	13.1	1.23	1200
Case 2	Preoperative	6.72	163	43	57	12.3	0.99	NA
	POD 1	6.86	177	553	601	14.6	1.13	30
	POD 3	6.98	130	280	130	17.6	1.22	25
	POD 5	7.33	110	124	51	22.4	1.20	10
	POD7	5.57	154	74	46	19.1	1.21	0
Case 3	Preoperative	2.79	81	36	53	12.5	1.12	NA
	POD 1	8.68	75	173	262	32.7	1.27	35
	POD 3	8.23	71	203	192	16	1.17	80
	POD 5	5.71	92	160	122	28.6	1.16	330
	POD7	4.18	107	119	71	21.3	1.03	10

Normal reference value: WBC count (3.50–9.50) $\times10^9$/L; PLT count (125–350) $\times10^9$/L; ALT 9–50 U/L; AST 15–45 U/L; TBIL 3.4–21 μmol/L; INR (0.8–1.2).
WBC, white blood cell; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; INR, international normalized ratio; POD, postoperative day.

Steiner grade III; and Ishak scores of 9 points for inflammation and 6 points for fibrosis (Table 2). All the three patients were treated with anti-hepatitis B drugs and administered with 0.8 g of sorafenib daily for anti-tumor treatment. Two months after discharge, the CT scan results showed no deterioration in case 1 (Figure 3A–C). Two months after hospital discharge, case 2 underwent TACE treatment. The patient then underwent CT scan 9 months after the operation (Figure 3D–F), and the result showed chest metastasis. He received conservative treatment in a local hospital and died 13 months after the operation. Meanwhile, case 3 underwent TACE treatment three months after hospital discharge. No metastasis or recurrence on MRI scan was found at 4 months after the surgery (Figure 3G–I). Tislelizumab is well tolerated as a tumor immune drug for patients with systemically treated unresectable tumors (13). Among the three cases, case 3 was treated with five courses of tislelizumab (200 mg). The two remaining patients did not receive tumor immunotherapy due to economic reasons. At the latest follow-up on March 1, 2022, cases 1 and 3 were still alive (Table 2).

Discussion

The incidence of HCC combined with PVTT is 44%–62.2%, and the prognosis is poor (14). The important basis for treatment of HCC with PVTT is the patient's PVTT classification. The two most widely used classification systems for PVTT are the Japanese VP classification (15) and the Chinese Cheng's classification (16). No global consensus or guidelines have been established on the diagnosis and treatment of HCC combined with PVTT (17). Chinese experts suggest that when the lesion is resectable and no extrahepatic metastasis is present, patients with type I/II PVTT should undergo surgical resection of HCC as well as adjuvant TACE therapy combined with sorafenib targeted therapy after the operation. For patients with Cheng's type III or VP4 whose tumor thrombus has invaded the main portal vein, treatment can be preoperative radiotherapy or TACE and surgery (18). European and American guidelines are based on the effect of surgical intervention on the survival and quality of life of patients and recommend conservative tumor-targeted drug therapy (4).

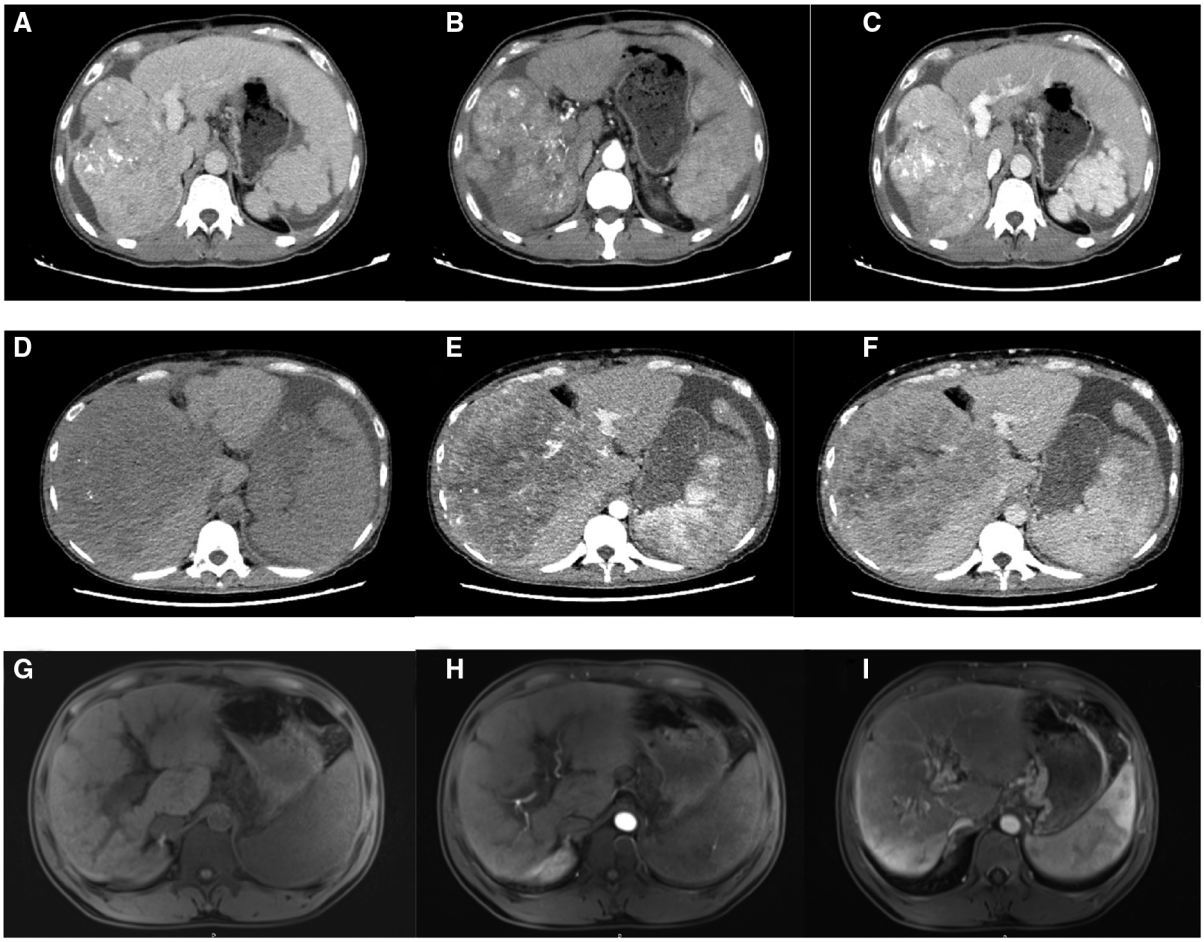

FIGURE 3
Postoperative CT images of case 1: unenhanced phase (A), arterial phase (B), and venous phase (C); postoperative CT images of case 2: unenhanced phase (D), arterial phase (E), and venous phase (F); and postoperative MRI images of case 3: unenhanced phase (G), arterial phase (H), and venous phase (I).

Increasing lines of evidence show that surgical treatment can improve the prognosis of patients with HCC combined with PVTT. A literature review shows that hepatic resection is the most effective therapy for patients with HCC and PVTT (19). Roayaie et al. (20) showed that for patients with large blood vessel invasion, Child–Pugh A liver function, and BCLC C stage who underwent surgical resection, the median survival time was significantly higher than that in patients who only used drugs. The 5-year overall survival and disease-free survival rates after Vp3–4 HCC hepatectomy are equivalent to those of Vp1/2 (21). In 2016, a national research in Japan showed that the median survival time of patients with Child–Pugh A of liver function who underwent surgical treatment was 1.77 years longer than that those who did not undergo surgery. Hence, surgical treatment has benefits on the prognosis of patients with HCC and PVTT regardless of age, tumor number, liver cancer etiology, tumor marker indicators, and other factors (22). The surgical treatment for HCC combined with PVTT is selected according to PVTT classification. Patients with Cheng's type I/II may achieve radical cure by removing part of the liver or hemiliver and the invaded portal vein branch. Tumor thrombi in patients with Cheng's type III/IV can be removed through the following: (1) removal of thrombus from the portal vein in the liver section; (2) portal vein resection and reconstruction of the portal vein invaded by tumor; and (3) thrombectomy of the portal vein stump and endovascular dissection (23). Deciding whether a patient can undergo surgery requires a comprehensive assessment of resectability. Many patients with HCC are already at an advanced stage at the time of diagnosis, and some of them have PVTT and intrahepatic metastasis or massive liver cancer. These patients are often unable to receive surgical resection due to insufficient FLR but can only receive TACE and drug therapy; however, their prognosis is generally poor.

ALPPS is a new surgical operation for patients with insufficient future liver remnant. Romic et al. (24) reported a case of successful ALPPS after unsuccessful double TACE procedure, thereby confirming the superiority of ALPPS. In addition, ALPPS has been used in patients with HCC combined with PVTT and insufficient FLR. Previously reported cases were all Cheng's type I/II or Vp2–3, and patients with Cheng's type III or VP4 undergoing tumor isolation through ALPPS have not been reported. The three cases in the present study were all Cheng's type III or VP4. We combined the characteristics of ALPPS technology to thoroughly remove portal vein tumor thrombi and then proceed with the isolation and ligation of the portal vein branches of the main side of tumor. Finally, the liver parenchyma was split.

CLAPT first deals with PVTT, which can avoid the metastasis and shedding of tumor thrombus caused by intraoperative operation as much as possible. The removal of the portal vein tumor thrombus can reduce the portal vein pressure and improve the patient's liver function and life quality. Even if radical tumor resection is not possible due to insufficient FLR growth or other reasons, liver parenchymal separation and portal vein branch ligation can substantially split the tumor, thereby controlling the growth and metastasis of tumors and tumor thrombi. Peng et al. reported that three patients with Cheng's type III or VP4 underwent priority portal vein thrombus removal and hemihepatectomy and had postoperative tumor-free survival time of 13, 9, and 4.6 years (25). Hepatectomy and thrombectomy cannot only avoid acute portal vein occlusion caused by tumor thrombus but also has certain survival benefits (26). This finding provides strong evidence for our research.

Although many Asian guidelines recommend surgical resection as the preferred method for treatment of HCC combined with PVTT, it still cannot be applied to all patients due to the limitations of the scope of indications and contraindications. Our research expanded the possible application range of surgical treatment in poor PVTT classification, but we still advocate comprehensive multimethod treatment for patients with HCC and PVTT. Matono et al. (27) reported that some VP4 cases received their first surgical resection combined with focal ablation or reoperation for a longer survival times. Kojima et al. (28) also reported that patients with VP4-type HCC had prolonged survival after surgery combined with TACE treatment. TACE is the most common treatment method for patients with HCC and PVTT who cannot undergo surgery. Patients with acceptable liver function and established portal collateral circulation can benefit from TACE (29). Sorafenib is an effective molecular targeted drug that is used to treat patients with advanced HCC. Sorafenib combined with TACE can significantly prolong the survival time of patients with unresectable HCC with PVTT compared with TACE alone (30). In the treatment of advanced liver cancer, immunotherapy has become popular among scholars. Immune checkpoint inhibitors targeting PD-1/PD-L1 and CTLA4 hold great prospects (31). In recent years, clinical trials of molecular targeted drugs combined with immunotherapy for the treatment of tumors have been vigorously carried out (32).

In this study, none of the three patients received conventional surgical resection of tumors. After CLAPT treatment, a follow-up anti-tumor comprehensive treatment should be conducted. During the follow-up, cases 2 and 3 underwent TACE surgery 2–3 months after the initial surgery; all the three cases took sorafenib after surgery. The statuses of cases 1 and 3 were great, and the survival periods were 41 and 21 months, respectively. Case 2 died of lung metastasis, and the overall survival period was 13 months. The survival time of the two tumor patients was more than 1 year, which was significantly longer than the median survival time reported in the literature for VP4 HCC with PVTT treated with TACE and sorafenib (3 months, $n = 10$) (30). Although the inclusion of a large number of cases was required in the study, the preliminary follow-up results confirmed the effectiveness of the new operation combined with the comprehensive treatment plan.

We combined the ALPPS technology to expand the indications for surgical treatment of HCC combined with PVTT. The three cases all had severe cirrhosis, and the preoperative FLR was less than 40%. Case 1 had transient acute kidney injury, which was gradually relieved after the comprehensive treatment, and the other cases recovered well after operation. Therefore, CLAPT may be a new and excellent treatment option for patients with advanced HCC complicated with PVTT, but this requires more case studies. We have registered a prospective clinical trial on CLAPT in the Chinese clinical trial registry (ID: ChiCTR2200060459) to validate its safety and efficacy.

Conclusion

We propose a novel modified surgical method for patients with advanced HCC combined with PVTT and expand the scope of surgical intervention in these patients, especially for patients with VP4 or Cheng's III type who cannot accept one-step hepatectomy. In the proposed method, the side of the liver containing the main tumor was split by removing the portal vein tumor thrombi combined with the ligation of the portal vein branch and the separation of liver parenchyma. This action contributed to the control of tumor growth and metastasis and improved the prognosis. These patients need to receive comprehensive multiple treatments postoperatively, such as immune and targeted drug therapy and TACE to further improve their survival time and quality of life.

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 Medical Ethics Committee of the First Affiliated Hospital of Guangxi Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZJ and GW collected and analyzed data and wrote the manuscript. BX, JW, and HZ contributed to the concept and design of the work. YG, MP, and TP revised the manuscript. ZW was responsible for the design of research ideas and the accuracy of all aspects of the 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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Lenvatinib combined with anti-PD-1 antibodies plus transcatheter arterial chemoembolization for neoadjuvant treatment of resectable hepatocellular carcinoma with high risk of recurrence: A multicenter retrospective study

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Background: Early recurrence is common after surgical resection (SR) for hepatocellular carcinoma (HCC) with high risk of recurrence and is associated with poor prognosis. The combinations of lenvatinib (LEN), anti-PD-1 antibodies (PD-1) and transcatheter arterial chemoembolization (TACE) (triple therapy) has shown better trend in tumor response and survival outcomes on unresectable HCC. It is unknown whether triple therapy for neoadjuvant treatment of resectable HCC with high risk of recurrence is effective. This article aimed to compare the outcomes of surgery alone and neoadjuvant combination treatment with triple therapy before SR in patients with HCC with high risk of recurrence.

Methods: A retrospective study was conducted on patients diagnosed with HCC with high risk of recurrence who received treatment with or without triple therapy. The records of 24 patients in the triple therapy group and 76 patients in the surgery-alone group were analyzed. Propensity score matching (PSM) was performed to minimize the influence of potential confounders.

Results: One hundred patients were enrolled. In the triple therapy group, 8 (33.3%) and 12 (50.0%) patients had complete and partial responses, respectively, as assessed by an investigator. Before PSM, the overall survival (OS) rates for the triple therapy group at 6, 12, 18, and 24 months were 100.0%, 100.0%, 100.0%, and 85.7%, respectively, compared with corresponding 92.1%, 73.7%, 53.9%, and 48.7% for the surgery-alone group (P<0.001). The disease-free survival (DFS) rates were 82.2%, 66.95%, 48.8%, and 48.8% for the triple therapy and 41.92%, 28.34%, 27.05%, and 22.99% for the surgery-alone group (P=0.003). After PSM, DFS and OS were significantly longer in the triple therapy group than in the surgery-alone group (DFS, p=0.019; OS, p=0.003).

Conclusions: Neoadjuvant combination treatment before SR had a high rate of tumor response and provided significantly better postoperative survival outcomes than surgery alone in patients with HCC with high risk of recurrence.

KEYWORDS

hepatocellular carcinoma, neoadjuvant treatment, triple therapy, disease-free survival (DFS), overall survival (OS)

Background

Hepatocellular carcinoma (HCC) is one of the most commonly diagnosed cancers and a leading cause of cancer-related death worldwide (1, 2). Surgical resection (SR) is the best choice for curative treatment of patients with HCC who have good functional liver reserves (3, 4). However, the inclusion criteria for selecting patients with HCC for SR remain controversial. In Western guidelines, resection is restricted to patients with early-stage HCC, which is based on the Barcelona Clinic Liver Cancer (BCLC) system classification (5). However, in China or Southeast Asia, it has adopted a more liberal application of SR for higher-burden HCC, including patients with large tumor size, tumor multiplicity, and portal vein tumor thrombus (PVTT) (6, 7). Moreover, many studies have indicated that patients with more advanced HCC would also benefit from SR as first-line therapy compared with nonoperative treatments, such as transcatheter arterial chemoembolization (TACE) and systemic therapy (8–11). However, SR for these patients with higher-burden HCC was associated with high rates of early recurrence and worse survival rates (12, 13). Therefore, effective treatments for patients with higher-burden HCC are urgently needed to reduce recurrence after SR and improve prognosis.

Presently, to reduce the tumor burden and improve the prognosis in patients with high risk of recurrence, neoadjuvant therapies have been performed before SR for many commonly occurring cancers, such as breast cancer, colon cancer, and esophageal cancer (14–16). Unlike these commonly occurring cancers, the use of neoadjuvant therapies for HCC with high risk of recurrence remains insufficiently effective (17). Several locoregional therapies, including TACE, have been used as neoadjuvant therapies for HCC with high tumor burden, but the clinical benefit was unsatisfactory (18–20). Until recently, multiple combinations of systemic therapies, including tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), have shown the potential to improve the prognosis of advanced HCC (21–23). Based on recent studies on combination therapy with several systemic therapeutic agents in advanced HCC, they might be potential candidates for neoadjuvant treatment before SR in patients with HCC with high risk of recurrence.

In our previous study, a combination of lenvatinib (LEN), anti-PD-1 antibodies (PD-1), and TACE (triple therapy) showed a high rate of tumor response and converted resection in patients with unresectable HCC (uHCC) with manageable toxicity (24). However, the effect of triple therapy as neoadjuvant treatment of

Abbreviations: HCC, Hepatocellular carcinoma; SR, surgical resection; LEN, lenvatinib; PD-1, anti-PD-1 antibodies; TACE, transcatheter arterial chemoembolization; PSM, Propensity score matching; BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombus; TKIs, tyrosine kinase inhibitors; ICIs, immune checkpoint inhibitors; CT, computerized tomography; MRI, magnetic resonance imaging; mRECIST, modified criteria; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; OS, overall survival; DFS, disease-free survival; PIVKA-II, vitamin K absence-II; HBsAg, hepatitis B surface antigen; MVI, microvascular invasion; AFP, α-fetoprotein; Tbil, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; TRAEs, treatment-related adverse events.

resectable HCC with high risk of recurrence is still unknown. This study aimed to investigate the safety and clinical efficacy of triple therapy in patients with HCC with high risk of recurrence.

Methods

Patients

The present study retrospectively reviewed patients with HCC patients with high risk of recurrence who received triple therapy (LEN+PD-1+TACE) before SR or underwent SR alone between November 2018 and December 2020 at four high-volume institutions: Fujian Provincial Hospital, Zhongshan Hospital of Xiamen University, First Affiliated Hospital of Xiamen University, and Zhangzhou Affiliated Hospital of Fujian Medical University. Baseline data, including preoperative, operative, and postoperative demographic details and outcomes, were retrospectively collected. This study was approved by the research ethics committee of each institution. All patients or their guardians provided written informed consent prior to enrolment.

The diagnosis of liver cirrhosis was based on the imaging of computerized tomography (CT) or magnetic resonance imaging (MRI). The diagnosis of HCC was based on biopsy or clinicoradiological criteria according to the guidelines proposed by the European Association for the Study of Liver (25). All HCC diagnoses were pathologically confirmed by two experienced pathologists after SR. In our study, HCC with high risk of recurrence was defined as follows: (1) HCC with Cheng's type II PVTT (PVTT involving the left- or right-side branch) (26), (2) single huge HCC (tumor size >10 cm) and tumors adjacent to the major vascular structures (including the main portal branches, main trunks of the hepatic veins, and inferior vena cava) leading to narrow-margin hepatectomy (resection margin <1 cm), and (3) unilobar multifocal disease (>3 tumors and one tumor >5 cm).

The key inclusion criteria were as follows: (1) age 18–70 years with good operative tolerance; (2) resectable primary HCC; (3) HCC with high risk of recurrence; (4) no distant metastasis; (5) the future liver remnant (FLR) of HCC patients with or without liver cirrhosis were ≥ 40% and 30% of the total liver volume respectively; and (6) Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–1. The exclusion criteria were as follows: (1) combined HCC and cholangiocarcinoma; (2) other serious malignant diseases; (3) Child-Pugh class C; (4) PVTT involving the bilateral or main trunk of the portal vein; (5) death of other disease-related causes; (6) any other previous antitumor treatment, such as radiofrequency ablation, radiotherapy, systemic therapy, and chemotherapy before SR; and (7) incomplete data.

Neoadjuvant triple therapy (LEN + PD-1 + TACE) and evaluation of response or toxicity

In the triple therapy group, the treatment period of neoadjuvant triple therapy was decided to 3 cycles in advance. Patients received LEN at a dose of 12 mg for body weight ≥60 kg or 8 mg for body weight <60 kg orally daily, and PD-1 at a dose of 200 mg sintilimab, 200 mg camrelizumab, 200 mg tislelizumab, 200 mg pembrolizumab, or toripalimab 240 mg intravenously every 3 weeks. TACE was performed within 7 days of diagnosis. Depending on the size, location, and arterial supply of the tumor, a mixture of iodized oil and pirarubicin was injected into the selected tumor artery through the microcatheter used for chemoembolization. Then, gelatin sponge particles were advanced toward the tumor-feeding arteries for selective embolization. Patients underwent a restaging scan and surgical evaluation every 4 weeks *via* the assessment of alpha-fetoprotein (AFP) levels and CT or MRI. LEN and PD-1 were discontinued for three days before and after TACE. SR was performed at least 3 weeks after the last dose of PD-1 and 1 week after the last dose of LEN. All patients with active HBV infection received oral antiviral treatment.

Tumors were assessed using modified criteria (mRECIST) both by the investigator and blinded independent central review (BICR) to evaluate the therapeutic effects of neoadjuvant triple therapy on primary HCC based on measurable diameter and arterial enhancement *via* enhanced CT or MRI. The categories of tumor response were as follows: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) using mRECIST. The objective response rate (ORR) was defined as the proportion of patients with CR or PR. The disease control rate was defined as CR, PR, and SD. Images were evaluated by two experienced readers, a radiologist and a surgeon, in consensus.

In the triple therapy group, after followed by 3 cycles of neoadjuvant triple therapy, the curative effect of HCC patients with high risk of recurrence was evaluated as SD, then these HCC patients would continue to be treated with neoadjuvant triple therapy until they were evaluated as PR or PD or neoadjuvant triple therapy was more than 12 months. After 3 cycles of neoadjuvant triple therapy, TACE was performed if there was an obvious hepatic arterial blood supply to HCC every 4–6 weeks according to the CT or MRI results. In the triple therapy group, when patients were evaluated as PD which was considered unsuitable for surgery, they were treated with nonsurgical therapy with regorafenib.

Pathologic CR was defined as complete absence of viable tumor cells, while major pathologic response was defined as ≤10% of viable tumor cells in the postoperative pathology.

Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events version 5.0.

Surgical procedure

In the surgery alone group, surgery was planned within 7 days of diagnosis. In the triple therapy group, patients with HCC were treated with triple therapy immediately within 7 days at the time of diagnosis and re-evaluated every 4 weeks after neoadjuvant triple therapy. In the triple therapy group, patients with HCC who were eligible for SR underwent definitive SR. When the tumor response was assessed as SD, surgery was planned after 3 months if the patients did not develop a contraindication to surgery. R0 resection was defined as histologically negative specimen margins, R1 as histologically positive margins, and R2 as macroscopically positive margins.

Follow-up

The primary endpoint was overall survival (OS), which was defined as the time from initial diagnosis to tumor-related death. One of the secondary outcomes was disease-free survival (DFS), which was defined as the time from the initial surgery to the time when a recurrent tumor was first diagnosed. The other secondary endpoints were ORR in the triple therapy group and the rates of microvascular invasion (MVI) and R0 resection after SR.

All patients were treated with TACE 4 weeks after SR. In the triple therapy group, the patients continued to receive LEN plus PD-1 for 4–12 months after SR. Follow-up was performed every 3 months with assessment of AFP levels, liver function, and double-phase helical CT or MRI. Recurrence was managed with multimodality treatments, including SR, radiofrequency ablation, TACE, or systemic therapy, based on the recurrence pattern and functional liver reserves. All patients were followed until death or the study end date of April 2022.

Statistical analysis

Statistical analyses were performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA), R3.1.2 software (Institute for Statistics and Mathematics, Vienna, Austria) and GraphPad Prism software (version 8.0; GraphPad Prism Software Inc., San Diego, CA, USA). Continuous data are presented as mean (s.d.) and analyzed using independent t-test. Categorical data were compared using the chi-squared test or Fisher's exact test. OS and DFS rates were calculated using Kaplan–Meier estimates and compared using the log-rank test.

Propensity score matching (PSM) analysis was performed to reduce possible selection bias using a 2:1 matching method using the package (MatchIt) *via* R3.1.2 software. Sex, age, hepatitis B surface antigen (HBsAg), liver cirrhosis, serum AFP, protein induced by vitamin K absence-II (PIVKA-II), tumor number, tumor diameter, ECOG PS, PVTT, and total bilirubin (Tbil), albumin (ALB), and alanine aminotransferase (ALT) levels were entered into the PSM.

Results

Patient characteristics

The baseline demographics and characteristics of the patients with HCC are shown in Table 1. A total of 100 patients with HCC with high risk of recurrence were included in our analysis, including 24 patients with HCC in the triple therapy group and 76 in the surgery-alone group (Figure 1). These patients were obtained from the Fujian Provincial Hospital (n=46), Zhongshan Hospital of Xiamen University (n=17), First Affiliated Hospital of Xiamen University (n=30), and Zhangzhou Affiliated Hospital of Fujian Medical University (n=7). Of the total patients, there were no significant differences in sex, age, HBsAg, liver cirrhosis, Child-Pugh class, AFP, PIVKA-II, tumor number, tumor diameter, ECOG PS, PVTT, ALB, ALT, and BCLC stage. Before PSM, the two groups showed a significant difference in Tibl level (> 23 μmol/L). After PSM, there were no significant differences in the Tibl level (> 23 μmol/L). In the triple therapy group, in one patient with PD, the PVTT was upstaged from Cheng's type II to type III and progressed with several new nodule formations, which was considered unsuitable for surgery and treated with nonsurgical therapy with regorafenib.

In the postoperative characteristics, the two groups showed a significant difference in MVI and R0 resection. There were no significant differences in the operative time and perioperative bleeding (Table 2).

Clinical responses and toxicity to neoadjuvant triple therapy (LEN + PD-1 + TACE)

The mean waiting time for liver resection in triple therapy group was 4.1 months (range, 1.9–12.4 months). The median number of TACE procedures was two (range, 1–5). The ORR of neoadjuvant triple therapy was 83.33% (20 of 24) by the investigator, with CR in eight patients, PR in 12 patients, SD in three patients, and PD in one patient, while 79.17% (19 of 24) by BICR, with CR in eight patients, PR in 11 patients, SD in four patients, and PD in one patient (Table 3). For all patients with HCC who received neoadjuvant triple therapy, reductions in tumor size were reported in 87.5% (21 of 24) of patients with evaluable HCC by the investigator using mRECIST (Figure 2).

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TABLE 1 Preoperative patient demographics and tumor characteristics.

Variables	Before PSM (n = 100)			After PSM (n = 69)		
	Surgery alone (n = 76)	Triple therapy (n = 24)	P-value	Surgery alone (n = 23)	Triple therapy (n = 46)	P-value
Sex			0.919			1.000
Male	64	20		38	19	
Female	12	4		8	4	
Age (years)			0.364			0.864
≤ 60	49	13		25	12	
> 60	27	11		21	11	
HBsAg			0.436			0.448
Yes	65	22		39	21	
No	11	2		7	2	
Liver cirrhosis			0.294			1.000
Yes	63	22		42	21	
No	13	2		4	2	
Child-Pugh class			0.701			0.612
A	74	23		45	22	
B	2	1		1	1	
AFP			0.444			0.601
≤ 400 ng/mL	32	8		19	8	
> 400 ng/mL	44	16		27	15	
PIVKA-II			0.772			0.693
≤ 400 mAU/mL	18	5		12	5	
> 400 mAU/mL	58	19		34	18	
No. of tumor			0.652			0.392
Single	34	12		19	12	
Multiple	42	12		27	11	
Tumor diameter			0.685			0.579
≤ 10 cm	19	7		15	6	
> 10 cm	57	17		31	17	
ECOG PS			0.079			0.154
0	75	22		45	22	
1	1	2		1	1	
PVTT			0.736			0.490
Yes	41	12		18	11	
No	35	12		28	12	
Tbil			0.045			0.178
≤ 23 umol/L	69	18		40	17	
> 23 umol/L	7	6		6	6	
ALB			0.663			0.606
≤ 40 g/L	31	11		19	11	
> 40 g/L	45	13		27	12	
ALT			0.508			0.730
≤ 50 U/L	53	15		26	14	
> 50 U/L	23	9		20	9	
BCLC stage			0.939			0.673
A	14	5		9	5	
B	21	7		19	7	
C	41	12		18	11	

(Continued)

TABLE 1 Continued

Variables	Before PSM (n = 100)			After PSM (n = 69)		
	Surgery alone (n = 76)	Triple therapy (n = 24)	P-value	Surgery alone (n = 23)	Triple therapy (n = 46)	P-value
CNLC stage			0.956			0.842
Ib	14	5		9	5	
IIa	10	4		10	4	
IIb	11	3		9	3	
IIIa	41	12		18	11	

Moreover, of the 23 patients who underwent successful SR, six had complete pathologic response, and four had major pathologic response. The treatment response of CR in imaging evaluated by BICR may not be PCR or MPR in pathology (Supplementary Table 1 and Supplementary Figure 1). There may be tumor survival in patients with CR in imaging evaluated by BICR. The treatment response of PR in imaging evaluated by BICR may be MPR in pathology.

The treatment-related adverse events (TRAEs) after neoadjuvant triple therapy are shown in Table 4. TRAEs occurred in 18 (75%) patients. The most common TRAEs were increased alanine aminotransferase level, decreased appetite, increased aspartate aminotransferase level, hypertension, hypothyroidism, diarrhea, increased blood bilirubin level, hand–foot skin reaction, decreased weight, and nausea and abdominal pain. None of the patients had grade 4 TRAEs, and all TRAEs were manageable after symptomatic therapy.

OS and DFS

The median follow-up duration was 19.3 months (6.4–24.0 months) in the triple therapy group. The follow-up duration was 24 months in the surgery-alone group. The 6-, 12-, 18-, and 24-month OS rates were 100.0%, 100.0%, 100.0%, and 85.7%, respectively, in the triple therapy group but 92.1%, 73.7%, 53.9%, and 48.7%, respectively (P<0.001; Figure 3A). The 6-, 12-, 18-, and 24-month DFS rates were 82.2%, 66.95%, 48.8%,

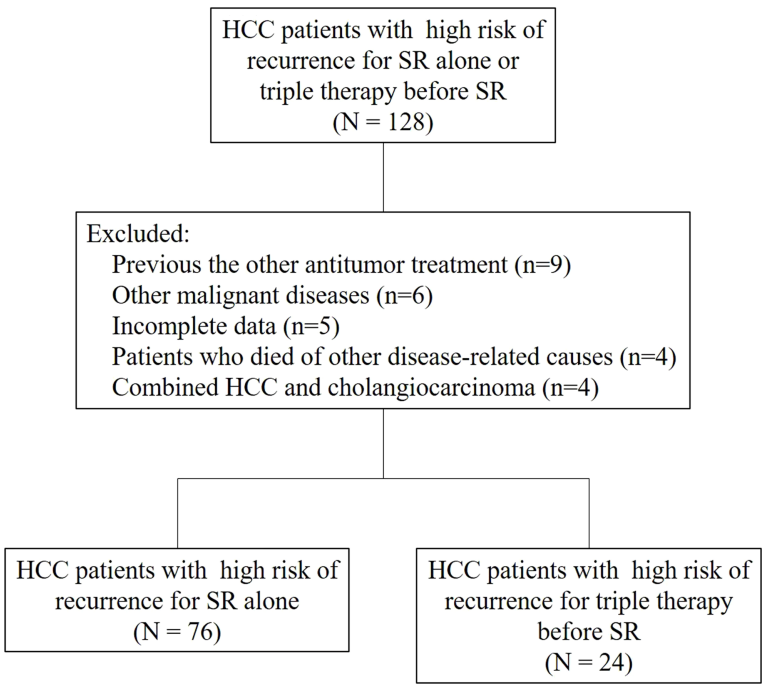

FIGURE 1
Flow diagram of the study selection process.

TABLE 2 Postoperative and intraoperative clinicopathological features.

	Surgery alone (n = 76)	Triple therapy (n = 23)	P-value
MVI			<0.001
Positive	67	6	
Negative	9	17	
R0			0.017
Yes	50	21	
No	26	2	
operative time, min	245 ± 8.40	221 ± 9.93	0.067
intraoperative bleeding, ml	775 ± 126.03	523 ± 98.05	0.207

and 48.8% respectively, in the triple therapy group and 41.92%, 28.34%, 27.05%, 22.99%, and 13.3%, respectively, in the surgery-alone group (P=0.003; Figure 3B). Neoadjuvant triple therapy significantly increased both OS and DFS rates in resectable HCC with high risk of recurrence. The recurrence patterns are presented in Table 5. There was no significant difference in recurrence patterns between the two groups. After PSM, OS and DFS were significantly longer in the triple therapy group than that in the surgery-alone group (OS, p=0.003; DFS, p=0.019 Figure 3C, D). In addition, there was trend toward improvement in DFS for patients with pathological CR and MPR; however, there were not significant differences in DFS and OS between patients with pathological CR and MPR or without pathological CR and MPR (Supplementary Figure 2). The reason for this result may be that the number of cases is too small and the follow-up time is not long enough. We still think pathological CR and MPR have better postoperative survival than those without pathological CR and MPR.

Discussion

This study indicated that the combination of LEN + PD-1 + TACE as a neoadjuvant triple therapy in resectable HCC with high risk of recurrence improved outcomes. Neoadjuvant triple therapy before SR aimed to downstage HCC and reduce tumor burden instead of surgery alone in patients with HCC with extremely large tumors, multiple primary tumors, or major vascular invasion. In our study, triple therapy showed a high ORR (83.3%) with manageable toxicity in resectable HCC with high risk of recurrence. Six patients (26.1%) had pathological CR, and four patients (17.4%) had major pathological response. Neoadjuvant triple therapy significantly increased both the OS and DFS rates in resectable HCC with high risk of recurrence, compared with surgery alone before and after PSM. In addition, triple therapy reduces the rate of MVI and results in margin-negative resections.

To date, tumor size, primary tumor number, narrow-margin hepatectomy, and macrovascular invasion have been proven as risk factors for poor prognosis in HCC after SR[12,13]. Therapeutic strategies for patients with HCC with these high risks of recurrence remain controversial in the West and East (5–7). In Western guidelines, patients with HCC patients with high risk of recurrence were considered to have advanced BCLC stage B or C, and systemic therapy or TACE was recommended (5). In contrast, SR is more frequently performed in patients with HCC, which would provide survival benefit, in China and Southeast Asia if they met the criteria for liver function (6, 7). However, many studies have indicated that the postoperative prognosis of patients with HCC with macrovascular invasion, huge HCC (tumor size >10 cm), and multiple HCC tumors was poor (12, 13). Moreover, when HCC is adjacent to the major vascular structures (including the main portal branches, main trunks of the hepatic veins, and inferior vena cava), surgeons have to peel

TABLE 3 Tumor Responses per Investigator and BICR Assessment.

Best Response, n (%)	Triple Therapy (n = 24)	
	Investigator	BICR
Complete response	8 (33.33%)	8 (33.33%)
Partial response	12 (50.00%)	11 (45.83%)
Stable disease	3 (12.50%)	4 (16.67%)
Progressive disease	1 (4.17%)	1 (4.17%)
Not evaluable	0	0
Objective response rate	20 (83.33%)	19 (79.17%)
Disease control rate	23 (95.83%)	23 (95.83%)

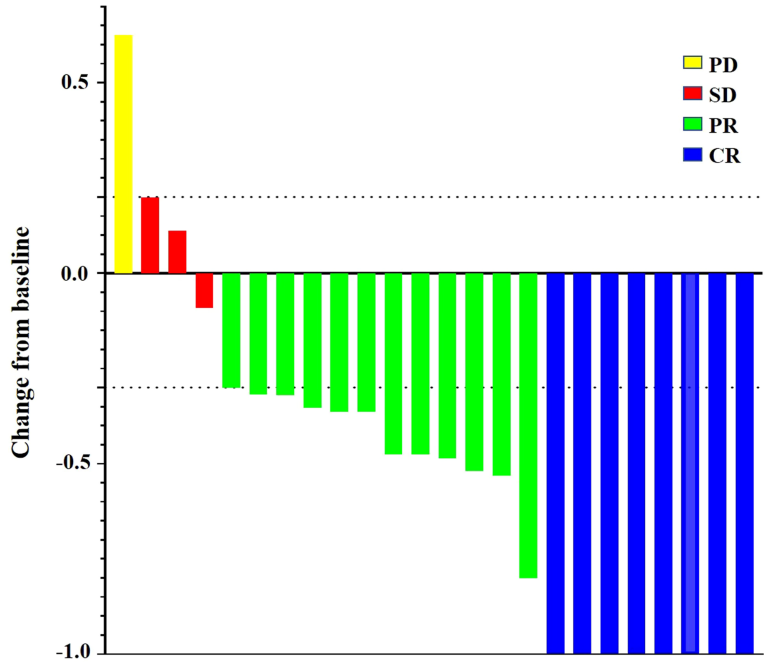

FIGURE 2
Percentage change from baseline in sums of maximum diameters of target lesions by the investigator using the mRECIST.

the tumor away from the vascular surface, leading to narrow-margin hepatectomy (RM <1 cm), and the surgical prognosis remains unsatisfactory due to a high risk of recurrence (27). Therefore, patients with advanced HCC may still be a controversial indication for SR.

To solve these problems, postoperative adjuvant or preoperative neoadjuvant therapy has been advocated to improve the postoperative prognosis of patients with HCC at high risk of recurrence. Numerous clinical trials have shown that the use of combination TKIs and ICIs has become a new standard of care option for uHCC (21–23). As for preoperative neoadjuvant therapy, in a single-arm phase 1b study, Ho indicated that the combination of cabozantinib and nivolumab in patients with HCC with borderline or locally advanced HCC as neoadjuvant therapy followed by SR is feasible and can result in margin-negative resections (17). A single-arm, open-label, phase 2 trial showed that neoadjuvant anti-PD-1 monotherapy in resectable HCC before SR resulted in a high rate of tumor pathological responses (28). Given the recent approval of several systemic therapeutic agents for HCC, it is possible that neoadjuvant therapy before SR in resectable HCC would improve surgical outcomes.

TACE is the standard treatment for intermediate-stage HCC (29). Studies have also indicated that TACE plus other treatment

TABLE 4 Most common treatment-related AEs in the triple therapy group.

Preferred AE Term	Any Grade	Grade 1	Grade 2-3
Increased alanine aminotransferase	13	10	3
Hypertension	10	4	6
Hypothyroidism	10	5	5
Diarrhea	9	7	2
Increased blood bilirubin	8	8	0
Hand–foot skin reaction	7	4	3
Fatigue	7	6	1
Weight decreased	6	3	3
Nausea	4	4	0
Abdominal pain	4	2	2

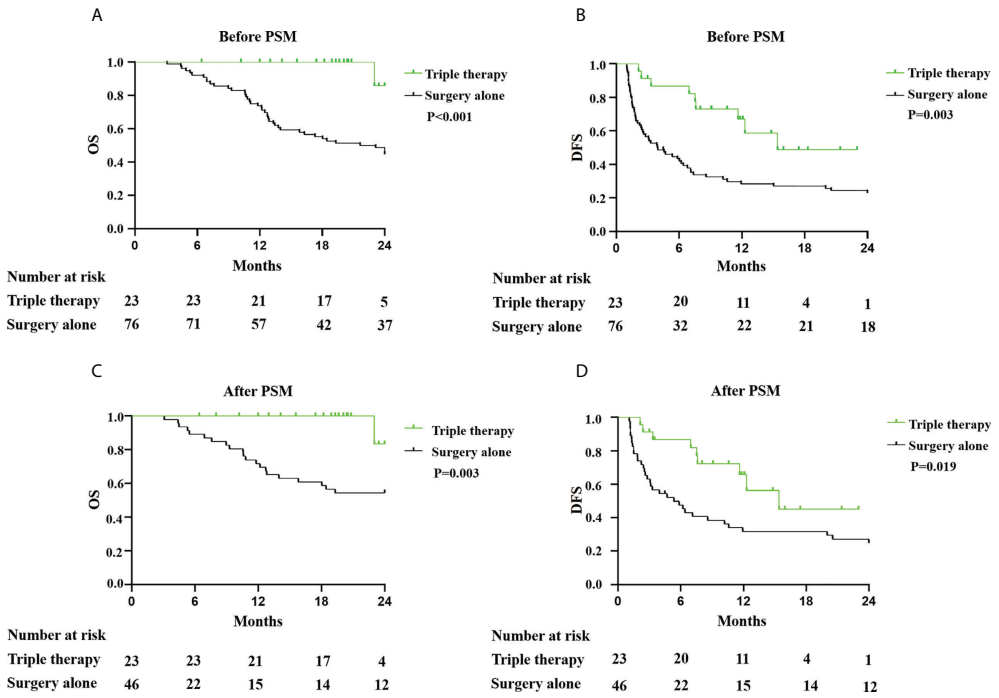

FIGURE 3
Kaplan–Meier analysis of OS and DFS in patients with HCC with high risk of recurrence treatment with triple therapy or surgery alone. **(A)** OS and **(B)** DFS in patients with HCC with and without triple therapy before PSM. **(C)** OS and **(D)** DFS in patients with HCC with and without triple therapy after PSM.

modalities, such as local ablation, radiation therapy, or systemic therapy, have been actively conducted and benefits patients with HCC (30, 31). Based on these findings, in our previous study, we showed that triple therapy in uHCC achieved a satisfactory ORR and was converted to resection[24]. Therefore, we assessed the effect of triple therapy, which was used as neoadjuvant therapy, in the treatment of resectable HCC with high risk of recurrence. Our results showed that triple therapy achieved a high ORR and significantly increased both the OS and DFS rates in resectable HCC with high risk of recurrence, compared with surgery alone. In our study, we also found that the triple preoperative neoadjuvant therapy reduced tumor size and MVI rate and improved R0 resection rate in HCC with high risk of recurrence, which would improve the prognosis. These confirms that the tumor is sensitive to the preoperative neoadjuvant therapy. Therefore, triple therapy may play a potential role in neoadjuvant therapy in the treatment of resectable HCC with a high risk of recurrence. However, more evidence needs to be accumulated.

Studies have shown that combination therapy with different treatment modalities may improve outcomes in HCC (24, 30). However, the mechanisms by which these modalities affect one another remain unclear. In triple therapy, PD-1 blocks PD-L1 to its receptor on T cells to suppress the proliferation and effector function of T cells to inhibit tumor growth (32, 33). However, it was not sufficient to initiate adequate levels of anticancer immunity in HCC *via* the PD-L1/PD-1 axis blockade alone (32, 33). TACE would enhance the clinical efficacy of PD-1 antibodies by activating the release of tumor-specific antigens (34). Unfortunately, TACE also creates a hypoxic microenvironment and activates the release of HIF-1 alpha, vascular endothelial growth factor, and fibroblast growth factor, leading to tumor angiogenesis and progression (34). LEN, a multikinase inhibitor of VEGF receptors 1-3, FGF receptors 1-4, platelet-derived growth factor receptor-a, RET, and

TABLE 5 Recurrence location after SR.

	Surgery alone	Triple therapy	P-value
Recurrence location			0.408
Intrahepatic	41	8	
Extrahepatic	6	0	
Intrahepatic and Extrahepatic	13	1	

KIT, could suppress tumor angiogenesis and antitumor immunity in tumor microenvironments, which would enhance the effect of PD-1 antibodies and TACE (30, 34). This is probably why triple therapy was associated with a high rate of tumor responses and was effective in improving the prognosis of patients with HCC with high risk of recurrence. However, further studies are required to elucidate the mechanisms of triple therapy.

This study had several limitations. First, this study had a retrospective design. Second, the number of patients with HCC treated with triple therapy (LEN+PD-1+TACE) is small. Third, surgical treatment and postoperative management were performed by different clinicians from different centers, which may have affected the surgical outcomes. Finally, the generalizability of our results may be limited because HCC in our study had a high proportion of HBV. Further prospective study should seek to resolve these issues.

Conclusion

In conclusion, neoadjuvant combination therapy with LEN +PD-1+TACE (triple therapy) before SR is associated with a high rate of tumor responses and is effective in improving the prognosis of patients with HCC with high risk of recurrence.

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 research ethics committee of Fujian Provincial Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceived and designed the research: M-LY and Ju-YW. Data acquisition: Ju-YW, Ji-YW, Y-NL, F-NQ, and S-QZ. data analysis: Ju-YW, Ji-YW, Z-YY, Y-FC, and BL. Drafting the manuscript: Ju-YW and M-LY. 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.985380/full#supplementary-material

SUPPLEMENTARY FIGURE 1
The corresponding IHC pictures and images in patients treated with triple therapy. **(A)** The treatment response of CR in imaging evaluated by BICR and PCR in pathology. **(B)** The treatment response of CR in imaging evaluated by BICR and not PCR or MPR in pathology. **(C)** The treatment response of PR in imaging evaluated by BICR and MPR in pathology.

SUPPLEMENTARY FIGURE 2
Kaplan–Meier analysis of OS and DFS in patients with PCR or MPR and without PCR or MPR in triple therapy group. **(A)** OS and **(B)** DFS in patients with patients with PCR or MPR and without PCR or MPR in triple therapy group.

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Clinical observation and risk assessment after splenectomy in hepatolenticular degeneration patients associated with hypersplenism

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Background: Both hepatolenticular degeneration (HLD) and viral hepatitis B (HBV) can cause hypersplenism, but whether splenectomy is needed or can be performed in HLD patients associated with hypersplenism is still controversial. At present, HLD combined with hypersplenism has not been listed as the indication of splenectomy.
Objective: This study aimed to investigate the efficacy, risks, and postoperative complications of splenectomy in HLD patients associated with hypersplenism.
Methods: We retrospectively analyzed the clinical data of 180 HLD patients with hypersplenism who underwent splenectomy in the Department of General Surgery, First Affiliated Hospital of Anhui University of Traditional Chinese Medicine, from January 2001 to December 2015. To evaluate the efficacy of splenectomy, the hemogram of white blood cells (WBC), red blood cells (RBC), platelets (PLT), and the liver function indexes including alanine aminotransferase, aspartate aminotransferase, and total bilirubin were recorded before surgery and 1, 3, 5, 7, and 14 days after surgery. In addition, the clinical data of 142 HBV patients with hypersplenism who underwent splenectomy over the same period were also recorded and compared with that of HLD patients. In particular, aiming to assess the risks of splenectomy in HLD, we also compared postoperative complications and 36-month mortality between the two groups.
Result: The level of WBC, RBC, and PLT were all elevated after splenectomy in both the HLD group and the HBV group. However, there was no significant difference in the variation of hemogram after splenectomy between the two groups ($P > 0.05$). Similarly, the variation of liver function indexes showed no statistical difference between the two groups. In terms of the incidence of postoperative complications including abdominal bleeding, pancreatic leakage, portal vein thrombosis treatment, incision infection, lung infection, and 36-month mortality, there were no significant differences between the two groups.
Conclusion: After splenectomy, the hemogram as well as liver function in the HLD group improved a lot and showed a consistent tendency with that in the HBV group. Meanwhile, compared to the HBV group, there was no significant difference in the incidence of postoperative complications in the HLD group.

All these results indicate that splenectomy in HLD patients combined with hypersplenism is completely feasible and effective.

KEYWORDS

hepatolenticular degeneration, hypersplenism, splenectomy, liver function, complication

Introduction

Hepatolenticular degeneration (HLD) was first described by Wilson in 1912 and is also known as Wilson's disease (1). It is a recessive genetic disease caused by copper transporter gene ATP7B mutation and results in excessive copper deposition, especially in liver tissue (2). The incidence of this disease is between 1:30,000 and 1:100,000 (3). According to the affected organs, the clinical manifestations of hepatolenticular degeneration differ, including liver function injury, nervous system, and mental performance (4, 5). Since the liver is the main organ of copper metabolism, chronic liver diseases are often the most common manifestations in patients with HLD (5). Some patients also present with hemolytic anemia and impaired renal function (6, 7). When copper accumulates in the liver to a moderate level, it will not only cause liver cirrhosis but also portal hypertension, which eventually develops to splenomegaly and hypersplenism (8).

At present, the main strategy for medical treatment is to remove copper, and the commonly used drugs for removing copper are mainly chelating agents D-penicillamine and tetrathiomolybdate (9–12), whose joint toxic and side effects are to inhibit the decline of whole blood cells caused by the bone marrow. Because these kinds of patients with hypersplenism have complete hemopenia, often internal medicine to remove copper is difficult to maintain. HLD is a congenital genetic disease, which requires lifelong cuprous removal treatment to achieve the same life span, life, study, and work as ordinary people. When liver transplantation is limited due to the shortage of donors, splenectomy to restore blood cells is often a necessary choice (13). The purpose of this study is to further evaluate the postoperative risk of splenectomy for HLD based on the observation of whether the splenectomy can achieve benefits and to provide support for the widespread implementation of this technique.

Previous studies have shown that splenectomy for portal hypertension caused by viral hepatitis is safe and reliable. Until now, no studies have examined and evaluated patients with HLD hypersplenism who underwent splenectomy. Therefore, we attempted to evaluate the safety and effectiveness of splenectomy for HLD patients by observing the differences in postoperative blood routine, liver function, and postoperative complications between the two groups.

Methods

Clinical research design

The clinical data of patients diagnosed with HLD combined with hypersplenism and undergoing splenectomy in the Department of General Surgery of the First Affiliated Hospital of Anhui University of Traditional Chinese Medicine from January 2001 to December 2015 were retrospectively analyzed. There were 98 males and 82 females in the HLD group, aged 19–57 years. All patients were diagnosed with HLD and hypersplenism before surgery. Liver function grading: 115 cases were grade A and 65 cases were grade B. In the viral hepatitis B (HBV) group, 142 patients were diagnosed with HBV and hypersplenism at the age of 15–87 years. Liver function grading: 87 cases were grade A and 55 cases were grade B, as shown in **Figure 1**.

The study has been approved by the Ethics Committee of the First Affiliated Hospital of Anhui University of Traditional Chinese Medicine and complies with the Helsinki Declaration Batch (Batch No.: 2019AH-32). All participants signed informed consent before collecting data.

Diagnostic criteria

(1) Diagnostic criteria for HLD. (a) Family genetic history: Parents are close relatives, compatriots with HLD patients, or those who die from unexplained liver disease. (b) Neuropsychiatric symptoms: slow progressive tremor, muscle stiffness, dyslexia, and liver symptoms. (c) Kayser–Fleischer ring on the cornea. (d) Ceruloplasmin level <1.6 μmol/24 h. (e) Liver copper concentration >250 μg/g (dry weight) (14).

(2) Diagnosis of hepatitis B. Based on clinical manifestations as well as serological and virological examinations (15).

(3) Child–Pugh grading criterion for liver function (16): serum bilirubin, ascites, serum albumin concentration, and prothrombin time were scored as 1, 2, and 3 according to different levels (mild level scored as 1, medium level as 2, and severe level as 3). Grade A was 5–6 scores, and the risk of surgery was low. Grade B was 7–9 scores, and the risk of surgery was medium. Grade C was 10–15 scores, and the risk of surgery was high.

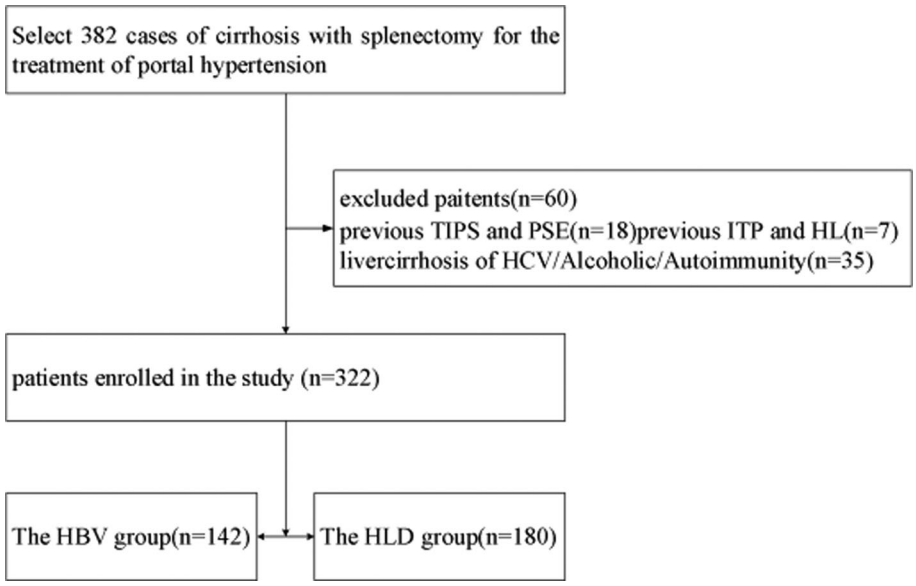

FIGURE 1
Diagram of the classification of patients who participated in this research.

Inclusion and exclusion criteria

Inclusion criteria: (1) diagnosed with hepatolenticular degeneration; (2) diagnosed with hypersplenism by color ultrasound, blood test, and bone marrow puncture; (3) Child–Pugh grade was A or B; (4) all included patients are willing to undergo surgery.

Exclusion criteria: (1) patients combined with hematopoietic system diseases, cardiovascular and cerebrovascular diseases, and hepatic and renal serious primary diseases, which are intolerant to surgery; (2) patients with neurological symptoms.

Therapeutic method

Preoperative preparation

Due to the suspension of normal anti-copper treatment during surgery, penicillamine and sodium dimercaptopropane sulfonate were applied to remove excess copper before surgery once the surgery date has been set. If the liver function still couldn't reach Child–Pugh grade A or B, transient use of glutathione, polyene phosphatidylcholine, and other liver-protecting drugs were applied. For those with abnormal coagulation function, 500 units of prothrombin complex were intravenously injected 30 min before surgery.

Anesthesia and surgical methods

All patients underwent open precise splenectomy. The specific surgical procedure is open the abdomen, separate the gastric colon and gastric spleen ligament, exposure and ligate the splenic artery, and autologous spleen blood reinfusion. Pull out the spleen with care, ligate the secondary and tertiary vessels at the upper and lower ends of the spleen one by one without blood, and then remove the spleen. While dividing the area around cardia, the high esophageal branches, collateral branches of paraesophageal veins, inferior phrenic branches, and peripheral vessels in the range of 6–8 cm in the lower esophagus were cut off. The wound was processed with hemostasis and suture serosa. Finally, a drainage tube was placed in the lower part of the spleen and the abdomen was closed layer by layer.

Postoperative treatment

(1) Conventional treatment: Postoperative anti-infection treatment, fluid replacement, nutritional support, hemostasis, and liver-protecting treatment.

(2) Treatment of postoperative complications. (a) Intraperitoneal hemorrhage treatment: Closely monitor the abdominal drainage and vital signs after surgery. Laparotomy is required under the condition that blood fluid in drainage is greater than 50 ml/h, hemoglobin level is less than 70 g/L with shock and other medical treatments are ineffective. (b) Pancreatic leakage treatment: Keep the drainage flow if complicated with fistula and grade B pancreatic leakage. Use somatostatin as appropriate if complicated with grade C pancreatic leakage. (c) Portal vein thrombosis treatment (PVST): Subcutaneous injection of low-molecular-weight heparin (LMWH) 4000 iu for 12 h, and urokinase 200 thousand bid. When thrombus ablation occurs and portal blood flow as well as platelet level are normal, keep the

subcutaneous injection of LMWH or warfarin oral administration for 3–6 months.

Observation index and detection method

(1) Blood routine detection: 5 ml of peripheral venous blood was extracted 1 day before the operation and 1, 3, 5, 7, and 14 days after the operation with an empty stomach. An automated blood cell analyzer (XN-9000, Sysmex) was applied to detect the level of white blood cells (WBC), red blood cells (RBC), and platelets (PLT) using the Coulter method.

(2) Liver function detection: 5 ml of peripheral venous blood was extracted 1 day before the operation and 1, 3, 5, 7, and 14 days after the operation with an empty stomach. An automatic biochemical analyzer (type 7600-010, Hitachi) was applied to detect alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels using the International Federation of Clinical Chemistry (IFCC) method, and total bilirubin (TB) levels with the Bromocresol Green (BCG) method.

(3) Postoperative complications and mortality:

(a) Abdominal hemorrhage. Postoperative bleeding was defined as a decrease of hemoglobin over 20 g/L after surgery. Postoperative observation of the drainage fluid color and clinical manifestations, and was confirmed by color Doppler ultrasound and CT (17). The formula for estimating intraoperative blood loss is described as (18): the total amount of liquid in the suction reservoir + (the weight of blood gauze and the net weight of gauze and normal saline) − the amount of flushing liquid.

(b) Pancreatic leakage. Pancreatic leakage was defined as the drainage fluid amylase being three times greater than serum amylase (19). Pancreatic leakage can be divided into three grades: grade A (biochemical leak)—only amylase is elevated without any clinical symptoms; grade B—clinical signs of infection and therapeutic measures should be changed; grade C—single or multiple organ dysfunction.

(c) Portal vein system thrombosis (PVST). Digital color ultrasonic diagnostic apparatus (Prosound α6) was used to detect whether thrombosis was formed in the portal system (the main portal vein, intrahepatic branch, mesenteric vein, and splenic vein) (20).

(d) Incision complications. Incision infection, bleeding, and dehiscence.

(e) Pulmonary and urinary infection. Diagnostic criteria for pulmonary infection: body temperature >37.5°C, white blood cell count $>10 \times 10^{10}$/L, and neutrophils >90%. Pulmonary imaging or CT examinations were consistent with infection (21). Diagnostic criteria for urinary infection: postoperative bacterial culture was positive (22).

(f) Mortality rate. Patients who died from surgery to discharge.

Statistical methods

Data analysis was performed using SPSS21.0 statistical software. The measurement data was expressed as $x \pm s$, and t-test was used when the data satisfy the normal distribution. Otherwise, the Wilcoxon rank sum test was used. Repeated measures of ANOVA or rank sum test (Mann–Whitney U) were used for the data of the two groups. The count data were expressed as the number of cases and percentages. The disordered classification data were analyzed by the x^2 test. The difference was considered to be statistically significant when $P < 0.05$. The end point time was defined as the period from the date of surgery to the date of death; otherwise, it was defined as censored data, calculated by Kaplan–Meier method using survminer and survival in R language, and performed log-rank test and plotted using ggplot.

TABLE 1 Comparison of general data of the two groups of patients.

Project	HLD ($n = 180$)	HBV ($n = 142$)	Statistics	P value
Gender [male/female, patients (%)]	98 (54)/82 (46)	81 (57)/61 (43)	$x^2 = 2.14$	0.14
Age (year)	47.47 ± 11.25	46.58 ± 13.41	$t = 0.65$	0.51
Child–Pugh [A/B, patients (%)]	115 (63)/65 (37)	87 (62)/55 (38)	$x^2 = 0.23$	0.62
BMI (kg/m^2)	24.15 ± 5.94	24.59 ± 5.89	$t = -0.60$	0.54
Diabetes [Y/N, patients (%)]	40 (22.2)/140 (78.2)	34 (23.9)/108 (76.1)	$x^2 = 0.13$	0.71
Hypertension [Y/N, patients (%)]	33 (18.3)/147 (81.7)	22 (15.5)/120 (84.5)	$x^2 = 0.45$	0.50
Ascites [Y/N, patients (%)]	68 (37.8)/112 (62.2)	45 (31.7)/97 (68.3)	$x^2 = 1.29$	0.25
Portal vein diameter (mm)	15.61 ± 1.59	15.23 ± 2.27	$t = 1.75$	0.08
Splenic vein diameter (mm)	6.22 ± 1.76	6.16 ± 1.97	$t = 0.29$	0.76
Operation time (min)	210.18 ± 16.51	205.90 ± 27.50	$t = 1.73$	0.08
Intraoperative blood loss (ml)	209.40 ± 17.46	206.57 ± 25.93	$t = 1.16$	0.24

HLD, hepatolenticular degeneration; HBV, viral hepatitis B; BMI, body mass index.

Results

Demographic characteristics

Data of 142 inpatients with hepatitis B and hypersplenism and 180 in patients with HLD and hypersplenism were analyzed. The mean age, sex, course of disease, and liver function grade of these patients are shown in Table 1.

Blood routine before and after splenectomy in two groups

By comparison, the white blood cell count, red blood cell count, and PLT count of the two groups were higher after the operation than before the operation ($P < 0.05$), and there was no difference in the WBC count between the two groups on the first, third and fifth day after operation ($P > 0.05$). On the 7th and 14th day after operation, the WBC count of HLD patients was higher than that of the HBV group ($P < 0.05$). The RBC count of the HLD group was significantly different from that of the HBV group 1 day after the operation ($P < 0.05$), but there was no difference at 3, 5, 7, and 14 days after the operation ($P > 0.05$). There was no difference in PLT count between the two groups on postoperative days 1, 3, 5, 7, and 14 ($P > 0.05$) (Figure 2).

Comparison of liver function before and after splenectomy in two groups

The ALT counts of the two groups were increased on the 1st and 3rd day after operation compared with those before operation ($P < 0.05$), and decreased on the 14th day after operation compared with those before operation ($P < 0.05$). There was no significant difference between the two groups at each time point ($P > 0.05$).

The AST count of the two groups was increased on the 3rd day after operation compared with that before operation ($P < 0.05$), and decreased on the 7th and 14th day after operation compared with that before operation ($P < 0.05$), and there was no significant difference between the two groups at each time point ($P > 0.05$).

The Total Bilirubin (TBIL) count of the two groups was increased on the 1st, 3rd, and 5th day after operation compared with that before operation ($P < 0.05$), and decreased on the 14th day after operation compared with that before operation ($P < 0.05$). There was a difference between the two groups on the 3rd and 5th day after operation ($P < 0.05$). There was no significant difference between the two groups on postoperative day 1 and day 14 ($P > 0.05$) (Figure 3).

Postoperative complications after splenectomy in two groups

As shown in Table 2, there was no difference in complications between the two groups ($P > 0.05$): one patient in the HLD group died due to ascites and liver function failure caused by portal vein thrombosis, and one patient in the HBV group died due to abdominal hemorrhage after surgery.

The two groups were followed up after splenectomy

After 36 months of follow-up, the mortality of HLD and HBV patients did not exceed the median survival time, and the postoperative follow-up cutoff survival rate of the two groups was 85.2% and 81.6%, the difference was not statistically significant (log-rank = 0.702; $P = 0.400$), as shown in Figure 4.

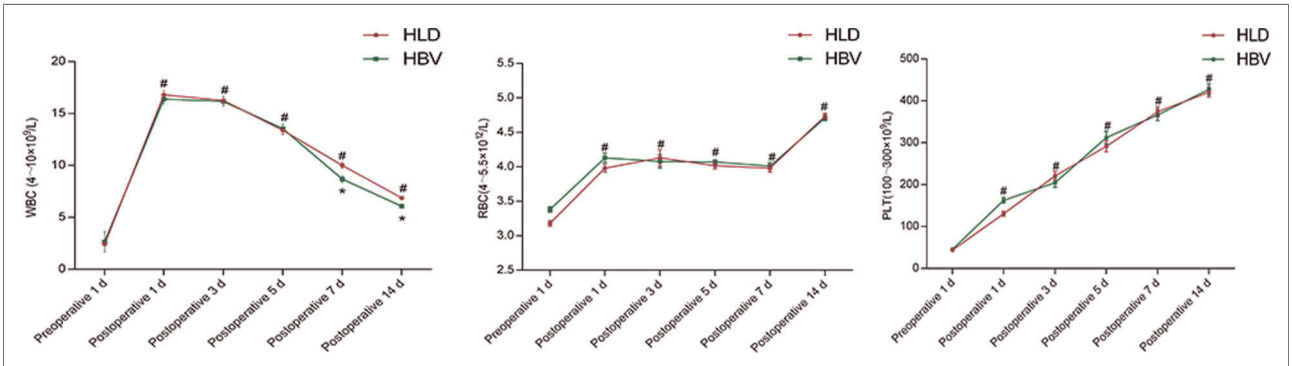

FIGURE 2
Blood routine before and after splenectomy in two groups. # refers to $P < 0.05$ compared with preoperative, * refers to the difference between the two groups at each time point $P < 0.05$, and ** refers to the difference between the two groups at each time point $P < 0.01$.

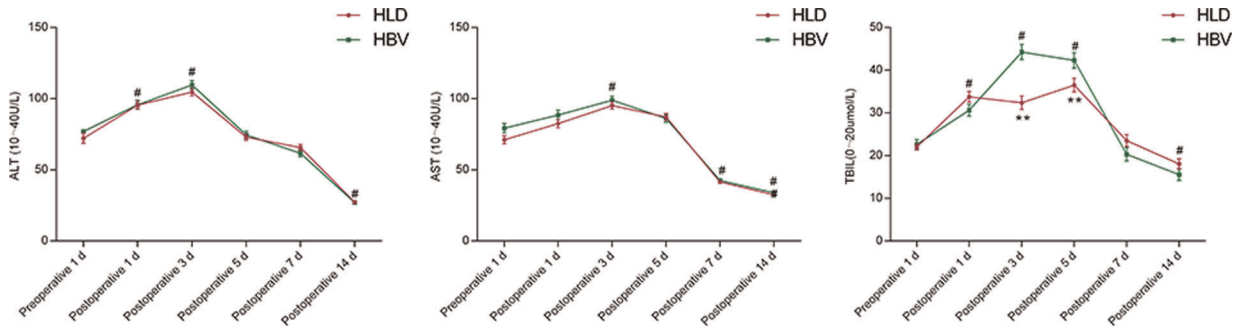

FIGURE 3
Comparison of liver function before and after splenectomy in two groups. # refers to $P < 0.05$ compared with preoperative, * refers to the difference between the two groups at each time point $P < 0.05$, and ** refers to the difference between the two groups at each time point $P < 0.01$.

TABLE 2 Comparison of complications after splenectomy in the two groups.

Complications	HLD ($n = 180$)	HBV ($n = 142$)	P^N
Abdominal bleeding	2	2	0.81
Pancreatic leakage	7	6	0.87
PVST	100	78	0.91
Incision infection	2	2	0.81
Pulmonary infection	3	3	0.76
Urinary tract infection	0	0	—

P^N refers to the postoperative time of main and in vivo effects in the group × the fixed time level of the group, and the differences in each level of individual effects in the group.
HLD, hepatolenticular degeneration; HBV, viral hepatitis B; BMI, body mass index; PVST, portal vein thrombosis treatment.

Discussion

The incidence of HLD in China is around 6/100,000, and our department is the largest HLD treatment center in China (23–28). In the beginning, we performed splenectomy in the pursuit to relieve hypersplenism, normalize blood cells level, and meet the requirement of lifelong anti-copper treatment. We have previously reported our experience and results in this regard (23–28). The expanded sample size of HLD patients involved in this work further confirmed that splenectomy can achieve the desired anti-copper effect and improve the blood cells level.

In the present observation, we have the following new findings: (1) RBC level increased a little after surgery, but the change was not statistically significant; (2) the level of WBC increased gradually from 1 to 7 days after splenectomy and decreased to the normal range from 7 to 14 days after splenectomy; (3) the level of PLT gradually increased from 1 to 14 days after surgery and reached a peak. Attention should be paid because there is a possibility of PVST formation if the PLT level is higher than 500×10^9/L. Generally, our clinical experience is continuously monitoring the level of PLT and D-dimer, meanwhile detecting PVST with digital color ultrasound. If the PLT level is higher than 500×10^9/L, then prophylactic anticoagulation treatment is needed. The detailed procedure was as follows: subcutaneous injection of low-molecular-weight heparin 4000 iu for Q12 h, and they maintain the treatment for 2–3 weeks after the PLT level returned to normal.

Except for the improvement of blood cells level, we have also noted that liver function was enhanced to varying degrees after splenectomy in HLD patients. Several different arguments are trying to clarify the underlying mechanism. Some studies focused on the secretion of IL-1, IL-6, TNF, TGF-β, and other cytokines due to splenomegaly, which leads to the formation of cirrhosis. Splenectomy can remove these cytokines and reduce inflammatory damage, thus promoting liver blood supply, and contributing to liver cell regeneration as well as resultant liver function improvement (29, 30). However, we are more convinced that the enhanced liver function is related to splenic artery steal syndrome, which refers to splenomegaly, splenic artery enlargement and thickening, blood flow acceleration, and other pathophysiological changes in patients with portal hypertension. Since both the splenic artery and the hepatic artery originate from the celiac trunk artery, the enlarged splenic artery and increased blood flow in the spleen will compete with the hepatic artery for the blood flow from the celiac trunk, resulting in the narrowing of the hepatic artery and the decrease of hepatic blood flow. Those changes ultimately result in an insufficient blood supply of liver tissue (normally more severe based on cirrhosis), liver cell damage, and hepatic dysfunction. After splenectomy, both hepatic blood supply and liver function will be promoted because of increased blood in the hepatic artery (31, 32).

The results of our study showed that the level of ALT and AST increased gradually 1–3 days after splenectomy, and decreased to normal 7–14 days after splenectomy. The level of

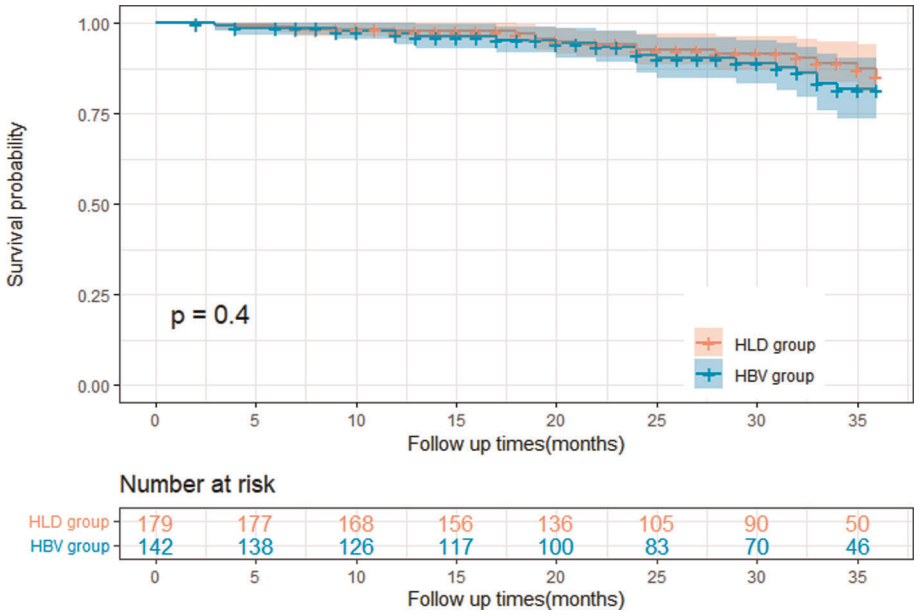

FIGURE 4
Comparison of mortality between two groups after 36 months of follow-up.

TB increased gradually 1–5 days after splenectomy and decreased to normal 7–14 days after splenectomy. Up to now, literature studies about splenectomy and liver function change are mainly focused on cirrhosis patients due to hepatitis or other etiology (33, 34), and few studies have been reported on liver function change after splenectomy in HLD patients. The present work can enrich relevant data in this field.

It has been reported that the mortality rate after splenectomy is 1.1%–1.63% (35, 36), and the complication rate is 12.9%. In our study, the mortality rate after splenectomy in the HBV group and the HLD group was 0.7% and 0.6% respectively, and there was no statistical difference in the mortality rate between the two groups. The incidence of postoperative complications in our results was higher than reported in literature studies because we focused on the complication of portal vein thrombosis. Notably, splenectomy in HLD patients does not result in increased mortality and is safe and feasible with relatively low surgical risk. In terms of postoperative complications and corresponding treatment, we would like to note: (1) hemorrhagic complications – the incidence of abdominal hemorrhage after splenectomy was 1.19% (37) as reported in the literature. This incidence was 1.4% in the HBV group and 1.11% in the HLD group, indicating that splenectomy in HLD patients will not increase the risk of bleeding. In this study, the incidence of abdominal hemorrhage in the HLD group was even lower than that reported in the literature and the HBV group, which may be related to (a) preoperative liver protection and prothrombin complex were used to improve the coagulation function, (b) intraoperative autologous splenic blood transfusion, making a large number of coagulation factors entering the body; precise splenectomy that performed during the operation also remarkably reduced the risk of bleeding, (c) postoperative application of liver protection and prothrombin complex to enhance the coagulation function. (2) Pancreatic leakage. Previously, we reported that the incidence of pancreatic leakage after splenectomy was 4.2% (28), as compared to 3.88% in the present study. The incidence of pancreatic leakage in HBV group and HLD group was 4.2% and 4.1%, respectively. The risk of pancreatic leakage was not increased after splenectomy in HLD patients. The treatment of pancreatic leakage differs according to varying situations. If complicated with fistula and grade B pancreatic leakage, then keeping the drainage flow is enough, and no need to use drugs for inhibiting pancreatic secretion. For patients with grade C pancreatic leakage and large drainage volume, somatostatin should be used appropriately. (3) (a) Complication of PVST. The incidence of PVST has been reported to be 24.6% (38) after splenectomy. In this study, the incidence of PVST in HBV and HLD groups was 54.92% and 55.55%, respectively. (b) Hazard of PVST. According to our observation, the hazard of PVST varies with the site of occurrence. The formation of complete PVST in the main portal vein or intrahepatic branch can not only show abnormal liver function indicators but also show clinical manifestations such as jaundice, ascites, hypoproteinemia, difficulty in wound healing or even incision dehiscence, which should be paid great attention to. PVST is formed in the

main part after intrahepatic branches, transaminase, and jaundice are often transient. The partial thrombosis in the mesenteric vein, with only abdominal distension, abdominal pain, decreased digestive function, and other gastrointestinal symptoms, is easily ignored or misdiagnosed as the gastrointestinal function has not been fully recovered after surgery. If complete obstruction occurs, intestinal congestion, intestinal obstruction, intestinal bleeding, and, in severe cases, intestinal necrosis and perforation. Splenic vein thrombosis is a common fever; we used to think of spleen fever as mostly caused by severe splenic vein thrombosis. Since the splenic vein formed after splenectomy is blind, it is usually not harmful to the body. (c) Prevention and treatment of PVST. It is found that there are high-risk factors for PVST formation, such as splenomegaly, portal vein diameter widened by preoperative examination, severe surgical trauma or traditional splenectomy, postoperative platelet elevation, and slow portal vein blood flow, and usually, preventive measures should be taken (39, 40). Based on the above data, the risk of postoperative PVST was not increased in the HLD group. Once PVST occurs, subcutaneous injection of low-molecular-weight heparin (LMWH) should be applied with a dose of 4000 iu for 12 h, and urokinase 200 thousand bid. When thrombus ablation happens and portal blood flow as well as platelet level are normal, keep the subcutaneous injection of LMWH or warfarin oral administration for 3–6 months. (4) Incision complications: It has been reported that the incidence of incision infection caused by splenectomy is 4% (41). In our study, the incidence of incision infection in the HBV group and the HLD group was 1.4% and 1.1%, respectively. Those results suggested that the risk of postoperative incision complications was not increased in HLD patients after splenectomy. To prevent HLD incision dehiscence, our experience is extending stitches removal to 12–14 days postoperatively. (5) Complications of systemic infection (lung and urinary tract). Literature studies reported that the incidence of pulmonary infection after splenectomy was 3.8% (37), and the incidence of urinary tract infection was 0.21% (42). In our study, the incidence of splenectomy for the HBV group was 2.11%, and the incidence of splenectomy in HLD was 1.66%. Based on the above data, splenectomy in HLD does not increase the risk of systemic infection complications. If systemic infection indeed happens, the assistance of a physician is usually needed. At 36 months of follow-up after splenectomy, there was no increase in postoperative mortality in HLD patients with hypersplenism. Although our finding has indicated that splenectomy for HLD complicated with hypersplenism is feasible and beneficial, the underlying molecular mechanism of liver function improvement, therefore, needs to be further studied through cell and animal experiments. Owing to our research being a single-center retrospective analysis, it is necessary to expand the sample size and conduct multicenter verification in the future.

Conclusion

Splenectomy in HLD patients combined with hypersplenism achieved the expected effects of enhancing blood cells and improving liver function. There was no increased risk of postoperative complications compared with splenectomy for HBV patients in the same period. Therefore, we conclude that splenectomy for HLD with hypersplenism is safe and feasible.

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

QY provided the ideas for the thesis. WZ wrote the thesis. ZZ collected the data. HP processed the data. FZ revised the thesis. 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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Comparison of Efficacy and Safety Between Laparoscopic and Open Radical Resection for Hilar Cholangiocarcinoma—A Propensity Score-Matching Analysis

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Background: Radical resection remains the most effective treatment for hilar cholangiocarcinoma (HCCA). However, due to the complex anatomy of the hilar region, the tumor is prone to invade portal vein and hepatic arteries, making the surgical treatment of HCCA particularly difficult. Successful laparoscopic radical resection of HCCA(IIIA, IIIB) requires excellent surgical skills and rich experience. Furthermore, the safety and effectiveness of this operation are still controversial.

Aim: To retrospectively analyze and compare the efficacy and safety of laparoscopic and open surgery for patients with HCCA.

Methods: Clinical imaging and postoperative pathological data of 89 patients diagnosed with HCCA (IIIA, IIIB) and undergoing radical resection in our center from January 2018 to March 2022 were retrospectively analyzed. Among them, 6 patients (4 were lost to follow-up and 2 were pathologically confirmed to have other diseases after surgery) were ruled out, and clinical data was collected from the remaining 83 patients for statistical analysis. These patients were divided into an open surgery group (n=62) and a laparoscopic surgery group (n=21) according to the surgical methods used, and after 1:2 propensity score matching (PSM), 32 and 16 patients respectively in the open surgery group and laparoscopic surgery group were remained. The demographic data, Bismuth type, perioperative data, intraoperative data, postoperative complications, pathological findings, and long-term survivals were compared between these two groups.

Results: After 1:2 PSM, 32 patients in the open surgery group and 16 patients in the laparoscopic surgery group were included for further analysis. Baseline characteristics and pathological outcomes were comparable between the two groups. Statistically significant differences between the two groups were observed in intraoperative blood loss and operative time, as it were 400-800 mL vs 200-400 mL (P=0.012) and (407.97 ± 76.06) min vs (489.69 ± 79.17) min (P=0.001) in the open surgery group and laparoscopic surgery group, respectively. The R0 resection rate of the open group was 28 cases (87.5%), and the R0 resection rate of the laparoscopic group was 15 cases (93.75%). The two groups showed no significant difference in terms of surgical approach, intraoperative blood transfusion, incidence of postoperative complications, and short- and long-term efficacy (P>0.05).

Conclusions: Laparoscopic radical resection of HCCA has comparable perioperative safety compared to open surgery group, as it has less bleeding and shorter operation time. Although it is a promising procedure with the improvement of surgical skills and further accumulation of experience, further investigations are warranted before its wider application.

KEYWORDS

laparoscopic hilar cholangiocarcinoma, open hilar cholangiocarcinoma, retrospective study, propensity score matching, R0 resection

Introduction

Radical resection remains the most effective treatment for hilar cholangiocarcinoma (HCCA) (1–4), and HCCA patients have a 5-year survival rate of less than 40% (1–3). Due to the complex anatomy of the hilar region and the high incidence of anatomical variations, HCCA is prone to invade portal vein and hepatic arteries, resulting in a low resectable rate and high surgical difficulty (4). In fact, successful laparoscopic radical resection of HCCA requires excellent surgical skills and rich experience. With the improvements in minimally-invasive surgical instruments, surgical skills, and accumulation of surgical experience, more patients have undergone laparoscopic or robotic radical resection of HCCA (5–11). Herein we retrospectively analyzed the clinical data of the patients who underwent radical surgery for HCCA in our center, and compared the efficacy of laparoscopic and open surgery for the patients with HCCA.

Materials and methods

Patients

We retrospectively analyzed the clinical data of 89 patients with a confirmed diagnosis of HCCA (IIIA, IIIB) by imaging [abdominal ultrasound, computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP)] and postoperative pathology who underwent radical resection in our center from January 2018 to March 2022. These patients were divided into open surgery (OS) group (n=62) and laparoscopic surgery (LS) group (n=21) according to the surgical modality used, 32 in OS group and 16 in LS group were finally included after 1:2 propensity score matching (PSM) (Figure 1). The demographic data, Bismuth type, perioperative data, intraoperative data, postoperative complications, pathological findings, and follow-up outcomes were compared between the two groups. This retrospective observational study was approved by the Medical Ethics Commission of our hospital (2022-r111-01) and was conducted in accordance with the Declaration of Helsinki and the *International Ethical Guidelines for Biomedical Research Involving Human Subjects.*

Preoperative management

Before the surgery, abdominal ultrasound, multidetector CT (MDCT), and MRCP were routinely performed in all patients to assess the extent of bile duct and blood vessel involvements and to determine whether the tumor was resectable. For resectable tumors, a three-dimensional (3D) visualization system was used to assess the presence (or absence) of anatomical variations in the bile ducts and vessels in the hilar region and calculate the

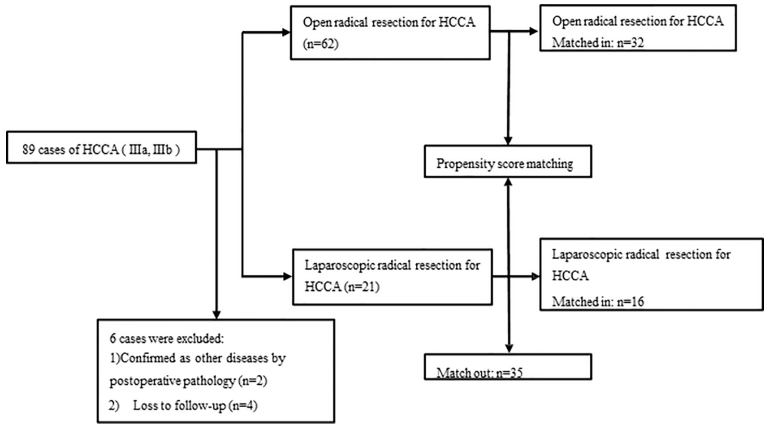

FIGURE 1
Flow chart of patient enrollment.

volume of the remnant liver. For patients with suspected lymph node metastasis, PET-CT was further performed to rule out any distant metastasis. For patients with a serum total bilirubin (TBil) level of higher than 100 mmol/L, percutaneous transhepatic biliary drainage (PTBD) was performed to lower TBil level and relieve biliary hypertension.

Surgical methods

Except for the different surgical approaches, both laparoscopic and open radical resection of HCCA followed the same surgical principles and resection criteria according to the guidelines (12). The scope of resection for Bismuth type III or IV HCCA included extrahepatic bile duct, left (or right) half of the liver, and caudate lobe, along with regional lymph node dissection. Anatomical liver resection was performed. To achieve R0 resection, we routinely resected the tumor and sent the surgical margins of proximal and distal bile duct for intraoperative frozen section analysis.

A careful exploration for ascites and peritoneal/omental metastases was performed first in both groups. Ultrasound was routinely performed to exclude intrahepatic metastases. An inverted L-shaped incision was created in the OS group, and a five-port approach was used in the LS group (Figures 2A, B). Patients were fasted for 12 h with water deprivation of 4 h before surgery. The operation steps in the LS group were as follows: 1) The lesser momentum was divided and the liver was suspended to expose the surgical field. 2) At the lower end of the common bile duct and at the upper edge of the pancreas, the surgical margin of lower bile duct margin was obtained for rapid intraoperative pathology. The upper end of the common bile duct was lifted. The lymphs, nerves, adipose tissue, and fibrous connective tissues in the hepatoduodenal ligament were removed during the operation (Figure 2C). 3) Stations 8 and 12 lymph nodes were dissected. After the outer sheath of the common hepatic artery was divided, the common hepatic artery was pulled with a thin silicone tube, and the gastroduodenal artery, proper hepatic artery, left and right hepatic arteries, and left and right portal vein branches were separated and skeletonized one after another (Figures 2D–H). 4) The Kocher incision was made for dissecting the lymph nodes around the head of the pancreas. 5) After removal of the gallbladder, the left or right hepatic artery and the left or right branch of the portal vein were severed, during which both the proximal and distal ends of the vessels were ligated with 10-gauge sutures, followed by the closure of the distal end with a plastic clip. In case of portal vein involvement, portal vein resection and reconstruction were performed (Figures 3A–C). 6) The blood flow into the liver was blocked using laparoscopic bulldog forceps, and intraoperative ultrasound was used to locate the middle hepatic vein, which was marked on the surface of the liver. The extent of liver resection was assessed preoperatively; accordingly, the left-half liver or right-half liver plus caudate lobe was resected *via* hepatic parenchymal transection-priority approach, during which the bile ducts and vessels, if encountered, were clamped using plastic clips or titanium clips and then disconnected. Subsequently, the half liver and caudate lobe were completely resected (Figures 3D, E). 7) The hepatobiliary ducts in liver remnant were identified and the surgical margins of the bile ducts were sent for rapid pathology. The hepatobiliary ducts in liver remnant were prepared for hepatobiliary duct-jejunum end-to-side anastomosis. 8) The jejunum was severed 20 cm below the ligament of Treitz. A side-to-side anastomosis was performed 50 cm below the proximal jejunum and distal jejunum, followed by the closure of the mesangial foramen. The distal jejunum and the colon were lifted anterosuperiorly for end-to-side Roux-en-Y hepaticojejunostomy with the bile duct in liver remnant, and

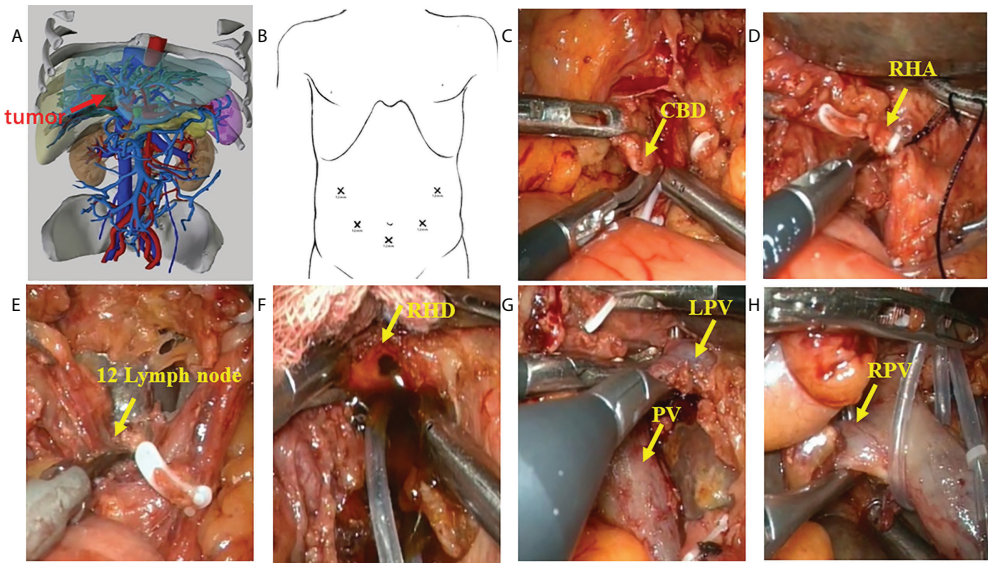

FIGURE 2
Procedure of laparoscopic hilar cholangiocrinoma 1. **(A)** three-dimensional (3D) imaging of the tumor (red arrow); **(B)** Trocar placement during laparoscopic radical resection for HCCA. The chief operator stands on the right side of the patient, inserting 5-mm and 12-mm trocars into the right abdomen; the first assistant stands on the patient's left side, placing 5-mm and 12-mm trocars above the umbilicus and on the left abdomen; and the camera-holder stands between the two legs of the patient(yellow arrow). **(C)** sever the lower end of the common bile duct at the upper border of the pancreas; **(D)** transect the right hepatic artery(yellow arrow); **(E)** dissect the lymph nodes in the hilar region(yellow arrow); **(F)** transect the right hepatic duct(yellow arrow); **(G)** identify the left branch of portal vein and portal vein (yellow arrow); **(H)** identify the right branch of portal vein (yellow arrow). CBD, Common bile duct; RHA, Right hepatic artery; RHD, Right hepatic duct; LPV, Left branch of portal vein; PV, Portal vein; RPV, Right branch of portal vein.

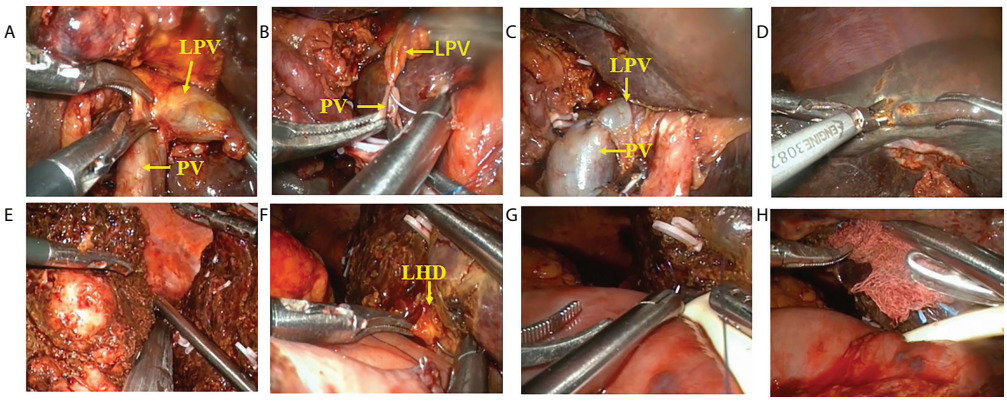

FIGURE 3
Procedure of laparoscopic hilar cholangiocrinoma 2. **(A–C)** resection and reconstruction of left branch of portal vein; **(D)** liver parenchyma transection-priority approach for liver resection; **(E)** transection of right hepatic vein using a cutter/staple; **(F–H)** hepatobliary duct-jejunum anastomosis (placement of T tube). LPV, Left branch of portal vein; PV, Portal vein; LHD,left hepatic duct.

biliary drainage tube was placed during the surgery in some patients (Figures 3F–H). 9) Abdominal drainage tubes were placed near the anastomosis site and liver section, respectively. Finally, the resected specimens and lymph nodes were sent for histopathological examinations.

Postoperative management

After the surgery, the patients were closely monitored in the surgical intensive care unit. Patients were given total parenteral nutrition before oral intake, according to the advice of the nutrition department. Prophylactic antibiotics, proton pump inhibitors (PPIs), and liver-protecting drugs were routinely administered. Generally, patients started a liquid diet on the postoperative day 3. The abdominal drainage volume was observed, and the possible bleeding or biliary fistula was evaluated. On day 5, all patients were re-examined with abdominal plain CT to identify whether there was ascites, and the abdominal drainage tube was taken out based on CT findings, color of drainage fluid, and inflammatory markers. In our center, the drainage tube was usually removed 6 - 8 days after operation.

Chemotherapy with gemcitabine or gemcitabine combined with cisplatin was recommended after discharge. All patients chose their chemotherapy protocols based upon their own willingness.

PSM

PSM is a useful statistical method for pre-processing data from observational studies and are widely used in retrospective studies to reduce the effects of confounding variables and other sources of bias, thus allowing for more reasonable comparisons between observational and control groups (13). In the present study, the LS and OS groups were compared using a 1:2 PSM to minimize differences among patient populations. Due to differences in baseline data, Logistic regression was used to calculate the propensity score of each patient; after 1:2 nearest neighbor matching, patients who did not meet the matching criteria were excluded.

Definitions

The common complications after radical resection of HCCA include intra-abdominal hemorrhage, stress ulcer bleeding, liver failure, ascites complicated with infection, bile leakage, biliary-enteric anastomotic stenosis, and delayed gastric emptying (DGE). The diagnosis of surgical site infection (SSI) was based on the criteria developed by the National Nosocomial Infections Surveillance System (NNIS), US Centers for Disease Control (14). The diagnosis of DGE was based on the definition suggested by the International Study Group of Pancreatic Surgery (ISGPS) in 2007 (15), i.e., a diagnosis of DGE can be made if one of the following conditions occurs after excluding mechanical factors such as anastomotic obstruction by upper gastrointestinal barium study or gastroscopy: a) the gastric tube needs to be indwelled for more than three days after surgery; b) the gastric tube needs to be re-inserted due to vomiting and other reasons after extubation; and c) solid food is still not allowed seven days after surgery. The short-term postoperative complications were graded using the 2004 Clavien-Dindo system (16). TNM staging was based on the eighth edition of the American Joint Committee on Cancer staging manual and tumor anatomic type was classified according to the Bismuth-Corlette system (17, 18).

Statistical analysis

Statistical analysis was performed using the SPSS 26.0 software package (SPSS Inc., IBM, Armonk, NY). The measurement data were first tested for normality and homogeneity of variance. The normally distributed or homogenous measurement data are presented using mean ± standard deviations and analyzed using t test or Chi-square test, otherwise they are presented using the medians (interquartile range) and analyzed using rank sum test. The count data are presented by the number of cases (percentage) and were analyzed using the Chi-square test, Chi-square test with continuity correction, or Fisher's exact test when appropriate. The Kaplan-Meier survival curves were used to compare the overall survival (OS) and disease-free survival (DFS) between these two groups. During PSM, Age, BMI, History of abdominal surgery, PTBD, ASA score, Bismuth type, and tumor diameter were used as covariates. the nearest neighbor matching method was used for 1:2 matching, and the caliper value was 0.1. All P values reported were two-tailed and a P value of <0.05 was considered significantly different.

Results

A total of 89 patients who had HCCA (IIIA, IIIB)and undergone radical HCCA resection were analyzed in this study, however six patients were excluded due to 1) confirmed as other diseases by postoperative pathology (n=2) and 2) lost to follow-up (n=4). Finally, 83 patients were included in this study, including 21 patients in the LS group and 62 patients in the OS group. After 1:2 PSM, 32 and 16 patients respectively in the OS and LS group were selected for further comparative analysis. We searched hospital electronic medical records to extract patient information, including demographic features, comorbidities, preoperative blood and imaging studies, tumor characteristics, intraoperative data, and postoperative data. Patients were followed up by phone or outpatient visits. Tumor recurrence and deaths were recorded.

Preoperative data

The preoperative data and pathological results of all patients are shown in Tables 1 , 2, respectively. There were no differences in terms of gender, age, body mass index (BMI), American Society of Anesthesiology physical status (PS) score, disease status, percutaneous transhepatic biliary drainage (PTBD), drinking and smoking histories, underlying diseases, biochemical tests, and history of abdominal surgery between the two groups (*P*>0.05). The Bismuth type, diameter, pathological differentiation, TNM stage, nerve invasion, microvascular invasion of the tumors, as well as the number of cleared lymph node and positive lymph nodes all showed no significant differences between these two groups (all P>0.05).

Intraoperative and postoperative data

The intraoperative and postoperative data are shown in Table 3. All surgeries were completed under laparoscope and none of them was converted to open surgery in LS group. The two groups showed no significant differences in terms of surgical approach, intraoperative blood transfusion, and incidence of postoperative complications (*P*>0.05). The intraoperative blood loss, operative time in the OS group and LS group had statistically significant differences which、 were 400-800) vs (200–400) mL (P =0.012), and (407.97 ± 76.06)min vs (489.69 ± 79.17)min (P=0.001), respectively.

Incision infection occurred in one patient in each group, which was improved after intensive dressing changes. In the OS group, one patient suffered from intra-abdominal hemorrhage, which was relieved after treatments such as cryoprecipitate infusion, improvement of coagulation function, and blood transfusion. Delayed gastric emptying (DEG, also known as gastroparesis) occurred in two patients in OS group and one patients in LS group, they were treated with gastrointestinal decompression, enhanced nutrition, and gastrokinetic drugs. In the OS group, two patients suffered from peritoneal effusion accompanied by intra-abdominal infection, which were improved after the placement of peritoneal catheter and the use of antibiotics; and three patients had pleural effusion, of whom one patient had pulmonary infection and was cured by

TABLE 1 Demographic and baseline characteristics in the OS and LS groups.

Variables	OS group (n = 32)	LS group (n = 16)	*P* value
Age [median (q1-q3), years]	62.5(52.25-67)	64(54-66)	0.991
BMI[mean ± SD,kg/m^2]	22.7 ± 2.71	23.54 ± 2.45	0.300
Gender, n (%)			0.683
Female	16 (50)	9 (56.25)	
Male	16 (50)	7 (43.75)	
ASA score, n (%)			0.781
1	20 (62.5)	9 (56.25)	
2	9(28.12)	6 (37.5)	
3	3 (9.38)	1 (6.25)	
Underlying diseases (heart disease, lung disease, diabetes, etc.), n (%)			0.911*
None	23 (71.88)	11 (68.75)	
Yes	9 (28.12)	5 (31.25)	
Smoking, n(%)	7 (21.88)	2 (12.5)	0.695*
Drinking, n (%)	5 (15.63)	2 (12.5)	0.885*
PTBD, n (%)	21 (65.63)	12(75)	0.509*
History of abdominal surgery, n (%)	5 (15.63)	4 (21.05)	0.885*
Biochemistry			
CA19-9[median (q1-q3), U/ml]	150.66(16.09-800)	135.74(50.94-587.83)	0.775
CEA[median (q1-q3), ng/ml]	4.13(2.2-6.26)	2.45(1.94-3.95)	0.094
CA125[median (q1-q3), U/ml]	18.95(11.8-28.5)	15.9(10.5-26.2)	0.548
AST[median (q1-q3), U/L]	95.9(55.28-167.53)	71.6(49.8-151.4)	0.484
ALT [median (q1-q3), U/L]	140.85(61.55-232.10)	123.00(43.00-180.50)	0.217
TBil[median (q1-q3), umol/L]	203.10(93.43-373.20)	227.00(87.30-317.40)	0.687
<34.2	6 (18.75)	1 (6.25)	0.470*
≥34.2	26 (81.25)	15 (93.75)	

Data are presented as standard deviation (mean ± SD), or as median (interquartile range), or as number (percentage). OS: Open Surgery; LS: Laparoscopic Surgery; BMI, Body Mass Index; ASA, American Society of Anesthesiologists; PTBD, Percutaneous Transhepatic Biliary Drainage; CA-199, Carbohydrate antigen 19-9; CEA, Carcinoembryonic antigen; CA125, Carcinoembryonic antigen 125; ALT, Alanine aminotranferease; AST, Aspartate aminotransferase; TBil, Total Bilirubin. *Fisher exact test.

TABLE 2 Pathological findings in the OS and LS groups.

Variables	OS group (n = 32)	LS group (n = 16)	*P* value
Bismuth type, n (%)			0.838
IIIa	15 (46.88)	7 (43.75)	
IIIb	17(53.13)	9 (56.25)	
Tumor diameter [mean ± SD,cm]	2.66 ± 1.04	2.58 ± 1.13	0.697
Degree of differentiation, n (%)			0.402
Well-differentiated	5 (15.63)	1 (6.25)	
Moderately-differentiated	12 (37.5)	9 (56.25)	
Poorly-differentiated	15 (46.88)	6 (37.5)	
TNM stage, n (%)			0.956
I	1 (3.12)	1 (6.25)	
II	8 (25)	4 (25)	
IIIA	6 (15.79)	2 (12.5)	
IIIB	6 (18.75)	52(12.5)	
IIIC	7 (21.88)	4 (25)	
IVA	4 (12.5)	3 (18.75)	
Perineural involvement, n (%)	11 (34.38)	6 (37.5)	0.831
Microvascular invasion, n (%)	1 (3.12)	1 (6.25)	0.798*
Lymph node involvement, n (%)			
Total number [median (q1-q3)]	6 (5 - 7)	7 (5 - 8)	0.146
Positive rate	7 (21.88)	7 (43.75)	0.217*

Data are presented as standard deviation (mean ± SD) or as median (interquartile range). * Fisher's exact test. OS, open surgery; LS, laparoscopic surgery.

thoracentesis catheter drainage and antibiotic treatment, and the other two patients were improved after drug adjustment. In the OS group and LS group, no patients developed liver failure or biliary leakage. In the LS group, one patients experienced pleural effusion accompanied by pulmonary infection, which was improved after medicinal treatment and functional training, and the other pulmonary infection patients were improved after drug adjustment; 1 patient suffered from intra-abdominal infection accompanied by ascites, which was improved after catheter drainage and antibiotic use (based on the results of bacterial culture). The hospitalization cost were 95697 (80306.25-117588.33) RMB versus 105170 (98160.05-119130) RMB and the postoperative hospital stay were 14(11.25-21.25) days versus 11.5(10.00-17.75) days respectively in the OS group and the LS group, with no statistically significant differences (*P*>0.05). One patient in the OS group died of gastrointestinal bleeding 2 months after operation. There was no statistically significant difference in readmission within 30 postoperative days (*P*>0.05).

Long-term outcomes

The long-term efficacy in the OS group and the LS group is shown in Table 4 and Figure 4. The median follow-up duration was 13.5 months in the OS group and 12 months in the LS group (P=0.303). Recurrence was noted in 4 cases (25%) in LS group, including three case of local recurrence (18.75%) and one case of distal metastasis (6.25%); in the OS group, ten cases (31.25%) progressed including five case of local recurrence (15.63%), and five cases of distal metastasis (15.63%). There was no statistical difference in the total recurrence rate, local recurrence rate, and distant metastasis rate between these two groups (P>0.05). During the follow-up period, seven patients (21.88%) in the OS group and three (18.75%) patient in the LS group died due to disease progression (P=0.999). The 1- year survival rates were 92.28% in the OS group and 91.67% in the LS group, and 2-year survival rates was 35.16% in the OS group and 34.37% in the LS group (P=0.536).The 1-year disease-free survival (DFS) rate was 82.16% in the OS group and 82.96% in the LS group, and the 2-year DFS rate was 38.64% in the OS group and 46.09% in the LS group (P=0.911).

Discussion

HCCA is an extremely destructive tumor that is difficult to diagnose and responds poorly to radiotherapy and chemotherapy. Complete tumor resection iscrucial for the long-term survival of patients with HCCA, in whom the 5-year survival rate is below 40% (1–4). However, due to the complex anatomy of the perihilar region and the high incidence of anatomical variations, HCCA is prone to invade the adjacent vessels, liver parenchyma, and pancreas, showing unique

TABLE 3 Intraoperative data and surgical effectiveness in the OS and LS groups.

Variables	OS group (n = 32)	LS group (n = 16)	*P* value
Operative time (mean ± SD, min)	407.97 ± 76.06	489.69 ± 79.17	0.001
Blood loss [median (q1-q3), mL]	600(400-800)	300(200-400)	0.012
Intraoperative blood transfusion, n (%)	24(75)	8(50)	0.083
Hepatectomy			0.838
Left hemihepatectomy + hepatectomy, n (%)	17 (53.12)	13 (56.25)	
Right hemihepatectomy + hepatectomy, n (%)	15 (46.88)	6 (43.75)	
Resection margin, n (%)			0.867*
R0	28 (87.5)	15 (93.75)	
R1	4 (12.5)	1 (6.25)	
Vascular resection and reconstruction, n (%)	2 (6.25)	1 (6.25)	0.527*
Complications, n (%)			
Clavien-Dindo grade < 3	25 (78.12)	14(87.5)	0.695*
Clavien-Dindo grade ≥ 3	7(21.88)	2(12.5)	
Incision infection	1 (3.12)	1 (6.25)	0.798*
Gastrointestinal hemorrhage	0 (0)	0 (0)	1.000*
Intra-abdominal hemorrhage	1(3.13)	0 (0)	0.721*
Delayed gastric emptying	2 (6.25)	1 (6.25)	0.527*
Pleural effusion	3 (9.38)	1 (6.25)	0.854*
Ascites	2 (6.25)	1 (6.25)	0.527*
Pulmonary infection	3 (9.38)	2 (12.5)	0.867*
Abdominal infection	2 (6.25)	1 (6.25)	0.527*
Liver failure	0 (0)	0 (0)	1.000*
Bile leakage	0 (0)	0 (0)	1.000*
Post-operative hospital stay [median (q1-q3),day]	14(11.25-21.25)	11.5(10.00-17.75)	0.254*
30-day readmission rate, n (%)	4 (12.5)	1 (6.25)	0.867*
90-day mortality rate, n (%)	1 (3.12)	0 (0)	0.721*
Hospitalization expenses [median (q1-q3),RMB]	95697(80306.25-117588.33)	105170(98160.05-119130)	0.213

Data are presented as standard deviation (mean ± SD) or as number (percentage). * Fisher's exact test. OS, open surgery; LS, laparoscopic surgery.

biological features. Thus, surgical treatment of HCCA is highly challenging (4). In recent years, laparoscopic technology has increasingly been applied in complex upper abdominal operations such as hepatectomy, radical gastrectomy, and pancreaticoduodenectomy, offering strong technical support and experience for laparoscopic radical resection of HCCA (19–22).

Since YU et al. (23) for the first time described the successful laparoscopic radical resection of HCCA in 2001, more similar cases have been reported. However, none of these reports involved the hemi-hepatectomy combined with caudate lobectomy. Gumbs et al. (24) reported minimally invasive treatment of extra-pancreatic cholangiocarcinoma, including 5 cases of minimally invasive resection of hilar cholangiocarcinoma, and 2 cases of laparoscopic extensive hepatectomy, with and postoperative recovery, achieving good curative effect.

Lee et al. (25) reported laparoscopic resection of HCCA in five patients, three of whom underwent hemihepatectomy combined with caudate lobectomy. In 2018, Zhang et al. (26)

TABLE 4 Long-term outcomes in the OS and LS groups.

Variables	OS group (n = 32)	LS group (n = 16)	*P* value
Followed-up duration [median (q1-q3), months]	13.5 (9.25_21.75)	12 (8.25 – 15.50)	0.303
Total recurrence rate, n (%)	10(31.25)	4 (25)	0.911*
Local recurrence	5 (15.63)	3 (18.75)	0.999*
Distant metastasis	5 (15.63)	1(6.25)	0.643*
Total mortality rate, n (%)	7 (21.88)	3 (18.75)	0.999*

#Wilcoxon signed rank test. *Chi-square test with continuous correction. OS, open surgery; LS, laparoscopic surgery.

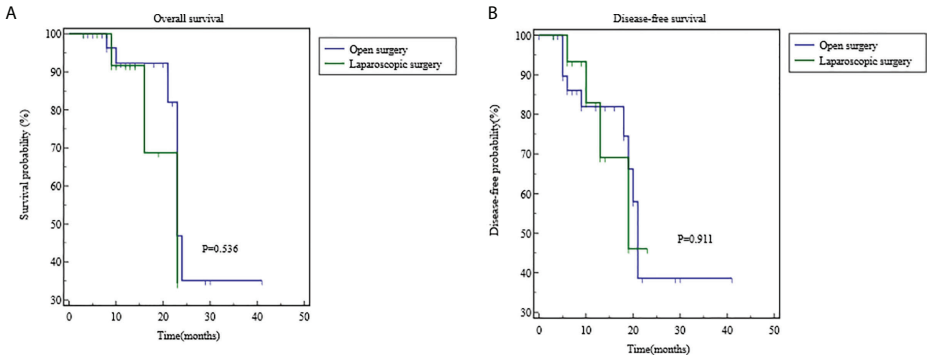

FIGURE 4
Comparisons of overall survival and disease-free survival using Kaplan-Meier curves. **(A)** the 1- year survival rates were 92.28% in the OS group and 91.67% in the LS group, and 2-year survival rates was 35.16% in the OS group and 34.37% in the LS group (P=0.536). **(B)** The 1-year disease-free survival (DFS) rate was 82.16% in the OS group and 82.96% in the LS group, and the 2-year DFS rate was 38.64% in the OS group and 46.09% in the LS group (P=0.911).

reported a similar case. However, all these were published in the form of case report, and did not compare the postoperative outcome. In 2019, Zhang et al. compared the performance of open versus laparoscopic radical resection in treating HCCA (6). It was found that there were no significant differences in postoperative hospital stay, blood loss, blood transfusion rate, and complications between these two groups. However, the laparoscopic group had significantly longer operative time as well as lower 1- and 2-year survival rates. Ratti et al. (27) compared the clinical data of HCCA patients undergoing laparoscopic or open radical resection and found that the laparoscopic group had less intraoperative blood loss, lower intraoperative blood transfusion rate, and shorter postoperative hospital stay than the open surgery group but with longer operative time; and there was no significant difference in R0 resection rate and postoperative survival time between these two groups. In 2021, Ma et al. (5) compared the laparoscopic versus open resection in HCCA patients and found that, in terms of long-term prognosis, the OS and DFS rates of the open surgery group were significantly higher than those of the laparoscopic group; however, the difference in the followed-up period between these two groups was statistically significant. The above reports are a comprehensive comparison of type I, II, III and open group, without separate clinical observation of laparoscopic and open surgery for type III. Laparoscopic completion of type I and type II is not controversial, and the operation is not difficult, but for type III, it is still controversial whether laparoscopy can be completed because of the difficulty of operation. This is a retrospective study on type III, having a large number of cases of type III, thus with more valuable observable results. It is found that compared with laparotomy, laparoscopy has no differences in the postoperative complications and postoperative survival rate. Moreover, its bleeding is lower than laparotomy. So, the laparoscopic surgery is safe and feasible, which is not wholly consistent with Ma et al. (5) report. The reason may be that the surgeon has experience in LPD500 cases, most of which were completed after 2019, achieving more R0 resection. Therefore, we primarily present our experience that having 150 cases of LPD and 50 cases of laparoscopic hemi-hepatectomy is the basic requirement for laparoscopic hilar cholangiocarcinoma, which can ensure not inferior to the laparotomy surgery complication.

In our retrospective observation, the operation time of the laparoscopic group was prolonged, which was statistically significant in terms of the comparison between the two groups. But it is expected that similar to LPD, this difference will be significantly shortened with the increase of proficiency. In addition, Sucandy I et al. (28) reported that 15 patients who underwent robot-assisted radical resection of hilar cholangiocarcinoma recommended that robotic technology should be considered as an alternative to “open resection”. Admittedly, robot has been widely used in liver surgery because of many advantages (29), and it is also one of the promising options for minimally invasive treatment of hilar cholangiocarcinoma. Although it is limited by its high price in China, we expect that it will be more widely used in the future.

Studies (30–32) have shown that R0 resection is the most important factor to achieve long-term survival in patients with HCCA, and a positive resection margin directly affects the prognosis of the patients. R0 resection requires negative surgical margins in multiple structures such as bile duct, liver, and blood vessels.

Tsao et al. (33) and Kow et al. (34–38) reported that the combination with caudate lobectomy raised the R0 resection rate

and prolonged patient survival. From a pathological perspective, Nimura et al. (32)also concluded that resection of the caudate lobe could benefit patients in long-term survival. At present, routine hemihepatectomy combined with caudate lobectomy has been widely recommended in the radical resection of HCCA (36–38). Unfortunately, most literature on the hemihepatectomy combined with caudate lobectomy for HCCA were retrospective studies (34–38) and therefore their findings were inevitably subjected to confounding factors. In the present study, the use of PSM enabled the comparability of the general data between two groups and increased the reliability of our findings.

In addition, although the preoperative assessment can improve our initial judgment of resectability, the final judgment needs to be made by the operator after intraoperative exploration. In cases where intraoperative exploration reveals vascular invasion on the side scheduled to be preserved and R0 may be achieved by the combined resection, hemihepatectomy combined with caudate lobectomy along with vascular resection and reconstruction may be performed (39, 40). In our series, portal vein involvement was found in one patient in each group, and a negative vascular margin was achieved after portal vein resection and reconstruction during the surgery. According to our experience, such operation can be done by experienced operators in large centers; if laparoscopic vascular resection and reconstruction is difficult to perform, timely intraoperative conversion to laparotomy is required to ensure surgical safety. Since laparoscopic hepatic artery resection and reconstruction is highly challenging and risky, along with questionable quality of the anastomosis, it should be carried out with caution (39).

Based on the R0 resection, standardized regional lymph node dissection is another important factor to ensure the long-term survival of patients with HCCA (41). Research has suggested that lymph node metastasis is an independent risk factor affecting the prognosis of patients with HCCA, and regional lymph node metastasis is a key predictor (41). Therefore, lymph node dissection in the perihilar region is a critical step in radical resection. However, due to the diverse techniques and concepts of radical resection among different medical centers, the optimal number of lymph nodes to be dissected also differs; accordingly, the optimal number of regional lymph nodes to be dissected is also inconclusive (42–44). According to our experience, at least 5 lymph nodes need to be dissected during the radical resection of HCCA, and the dissection range should include the lymph nodes and nerve plexus tissues in hepatoduodenal ligament, near the common hepatic artery, and behind the head of the pancreas. All of these tissues except the hepatic artery and portal vein must be resected to achieve the skeletonized dissection. In the present study, there was no statistical difference in the total number of dissected lymph nodes between the LS group and the OS group.

Notably, peripheral blood vessels should be carefully protected during lymph node dissection. According to Zhang et al. (6), excessive dissection of lymph nodes around the hepatic artery resulted in mechanical damage to the blood vessels, leading to postoperative pseudoaneurysm of the hepatic artery. With the maturity of laparoscopic liver resection and pancreaticoduodenectomy, laparoscopic hilar lymph node dissection has increasingly been applied. Using intrathecal separation and dissection techniques, the laparoscopic procedure minimizes the direct clamping of blood vessels with surgical instruments. Preferably, a vessel loop is used to suspend and stretch the vessel, so as to minimize the damage to the intima of the arteries and prevent serious complications such as postoperative aneurysm. If lymph node station 13 is found to be positive by intraoperative rapid pathology, station 16 should be dissected and sent for rapid pathology. If the result is also positive, radical resection should be abandoned.

In the present study, there was no statistically significant difference in perioperative safety between the LS and the OS group. We believe that laparoscopic radical resection of HCCA will be increasingly adopted with the improvements in surgical skills and accumulation of experience. However, it remains a challenging and high-risk technique in its initial stage and should be performed only in carefully selected patients in large hepatobiliarypancreatic surgery centers. With patient safety as the top priority, the surgical procedures should be standardized to ensure surgical safety and prolong the long-term survival.

Based on our experience, Surgical indications of laparoscopic radical resection for hilar cholangiocarcinoma were as follows: ① hilar cholangiocarcinoma(I, II) and part hilar cholangiocarcinoma (IIIa, IIIb)(no invasion to points U or P, preferably no invasion to the secondary bile duct branches) and sufficient residual liver volume after tumor resection was clearly diagnosed without signs of distant metastasis based on preoperative imaging and biochemical tests; ②the tumor did not invade key peripheral blood vessels such as the portal vein and hepatic artery and did not require combined vascular resection; ③no severe multiple organ dysfunction such as heart, lung, kidney and brain, or combined with underlying diseases can tolerate surgery after active adjustment. In our experience, if there are both more than 10 cases of experience in laparoscopic pancreaticoduodenectomy combined with vascular resection and reconstruction and more than 10 cases of laparoscopic radical resection of hilar cholangiocarcinoma, the hilar cholangiocarcinoma combined with vascular resection and reconstruction can be tried.

Our study had some limitations. First, as a retrospective study, it lacked prospective design and randomization. Although PSM was used, it could not fully rule out the confounding factors, and there were certain biases. Second, the sample size was small. Thus, prospective multi-center clinical studies with large sample sizes are needed to further validate the safety and

effectiveness of laparoscopic radical resection of HCCA and standardize its surgical steps.

Conclusion

In summary, this retrospective observational analysis demonstrated that laparoscopic radical resection of HCCA is safe in the perioperative period and can be performed in large hepatobiliarypancreatic surgery centers after careful assessment. Our results showed that the efficacy of LS group was comparable to that of OS group, we are confident that the long-term efficacy of this technique will be dramatically improved with the improvements in surgical skills, accumulation of experience and prolonged follow-up period.

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

Written informed consent was obtained from the patient for publication of this report and any accompanying images.

Author contributions

Y-GH, Y-ML, X-BH and LZ contributed to conception and design of the study, and drafted the manuscript. JL, F-XY, L-QL, X-HP, WH, C-LD and Y-CT contributed to analysis and interpretation of data and revised the manuscript. WH, QR and Y-GH participated in clinical treatment operation and literature research. 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.

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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.2022.1004974/full#supplementary-material

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Laparoscopic vs. open anatomical hepatectomy for intrahepatic cholangiocarcinoma: A retrospective cohort study

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Background: Intrahepatic cholangiocarcinoma is a highly malignant and invasive cancer originating from biliary epithelial cells. The current study was designed to evaluate the feasibility, safety, and clinical outcomes of laparoscopic anatomical hepatectomy in patients with intrahepatic cholangiocarcinoma.

Methods: After screening, 95 patients who underwent anatomical hepatectomy for intrahepatic cholangiocarcinoma at our center were enrolled and divided into two groups according to the surgical approach; the baseline characteristics, pathological findings, surgical outcomes, and long-term outcomes were compared. Moreover, univariate and multivariate analyses were performed to identify independent prognostic factors for overall survival (OS) and disease-free survival (DFS).

Results: There were no significant differences in baseline characteristics or pathological findings between the two groups. Regarding short-term outcomes, the intraoperative blood loss, incision length, and length of postoperative hospital stay were more favorable in the laparoscopic anatomical hepatectomy group than the open anatomical hepatectomy group ($P < 0.05$). The two groups differed significantly in the extent of liver resection, with a lower lymph node dissection rate and lymph node yield in the laparoscopic anatomical hepatectomy group ($P < 0.05$). Furthermore, the postoperative complication rate was similar in the two groups ($P > 0.05$). The median postoperative follow-up times were 10.7 and 13.8 months in the laparoscopic anatomical hepatectomy and open anatomical hepatectomy groups, respectively. Regarding the long-term follow-up results, OS and DFS

Abbreviations
ICC, intrahepatic cholangiocarcinoma; LAH, laparoscopic anatomical hepatectomy; OAH, open anatomical hepatectomy; CT, computed tomography; MRI, magnetic resonance imaging; ICU, intensive care unit; BMI, body mass index; OS, overall survival; RFS, recurrence free survival; HR, hazard ratio; CI, confidence interval; LND, Lymph node dissection; LH, laparoscopic hepatectomy; LLR, laparoscopic liver resection

were similar in the two groups ($P > 0.05$). On multivariate analysis, the independent prognostic factors for OS were CA-199, CEA, HGB, tumor diameter, and T stage, and those for DFS were CA-199 ($P < 0.05$), and T stage ($P < 0.05$).

Conclusion: laparoscopic anatomical hepatectomy for intrahepatic cholangiocarcinoma is safe and feasible when performed by experienced surgeons. Compared with open anatomical hepatectomy, laparoscopic anatomical hepatectomy provides better short-term outcomes and a comparable long-term prognosis.

KEYWORDS

laparoscopic anatomical hepatectomy, open anatomical hepatectomy, outcomes, overall survival, disease-Free survival

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a type of cancer originating from biliary epithelial cells, accounting for approximately 5%–10% of primary malignant liver tumors and representing the second most common primary malignant tumor of the liver after hepatocellular carcinoma (1, 2). Moreover, ICC is highly malignant and invasive, with a high relapse rate and poor prognosis. Currently, hepatectomy is considered the primary choice for managing ICC.

Hepatectomy performed in patients with ICC can be divided into anatomical and nonanatomical hepatectomy; anatomical hepatectomy refers to complete resection of the liver segment affected by the tumor on the basis of the Couinaud classification (3). Many studies have found that anatomical hepatectomy is superior to nonanatomical hepatectomy in terms of postoperative survival, complication, and recurrence rates regardless of whether open and laparoscopic surgery is performed (4, 5). Nonetheless, laparoscopic anatomical hepatectomy (LAH) also has several limitations compared with open anatomical hepatectomy (OAH), such as the narrow operating space, and the difficulty in intraoperative bleeding control, all of which bring more challenges to LAH (6). Although there have been many studies comparing LAH with OAH (7), no studies comparing LAH with OAH for ICC have been performed. In addition, ICC is higher invasion, higher recurrence rate and higher mortality compared to hepatocellular carcinoma (HCC), anatomical hepatectomy is more suitable for ICC. To further evaluate the safety and efficacy of LAH for ICC, we retrospectively analyzed 30 patients who underwent LAH and OAH for ICC at our center and compared the short- and long-term outcomes of the patients. In addition, a risk factor analysis was conducted to evaluate the independent prognostic factors for long-term outcomes.

Materials and methods

Patients

Between March 2011 and April 2021, a total of 172 consecutive patients underwent hepatectomy for ICC at Qilu Hospital of Shandong University in Jinan (China). The inclusion criteria for our study were as follows: (1) patients who underwent potentially curative resection, defined as complete tumor resection without macroscopic residual tumor tissue, with R0 or R1 surgical margins, and without evidence of distant metastases; (2) patients with ICC confirmed by postoperative pathology; (3) patients who underwent anatomical liver resection; and (4) patients with complete clinical information available. While the exclusion criteria were (1) patients did not undergo radical resection or anatomical resection; (2) The pathological type was not ICC; (3) Incomplete clinical data. After screening, 95 patients who underwent anatomical hepatectomy were finally included in our study. These patients were divided into the LAH group ($n = 30$) and OAH group ($n = 65$) according to the surgical procedure. All of the data used in this study were obtained from our hospital database and anonymized during the study. This study complied with the Declaration of Helsinki (World Medical Assembly) and its amendments and was approved by the Ethics Committee of Qilu Hospital, Shandong University (approval number: KYLL-202011-180).

Preoperative preparation

Preoperatively, the patients were given the necessary supportive therapy, such as liver protection therapy or oral antiviral therapy, to improve their liver function reserve. All patients underwent contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) before surgery to assess tumor characteristics (morphology, size, number, and location) and to provide guidance for the surgical plan, as well as for the assessment of the patient's residual liver volume.

Surgical technique

All patients were placed in the supine position after general anesthesia was administered. Routine surgical disinfection and draping were performed. For LAH patients, pneumoperitoneum

was routinely established before the surgical procedures, and the pressure was maintained between 12 mmHg and 15 mmHg. OAH was performed through an inverted L-shaped incision in the upper left abdomen, measuring approximately 20–25 cm.

The surgeon performed LAH and OAH following the same standardized surgical principles. After entering the abdominal cavity, the abdominal organs were examined to exclude abdominal metastases, and then the tumor location was assessed to determine the surgical plan. Tumors in superficial locations could be judged by the naked eye, while tumors in deeper locations could be judged by intraoperative ultrasound and other equipment. Subsequently, the liver to be resected was fully mobilized by releasing its surrounding ligaments according to the surgical plan. Before liver resection was performed, a tourniquet was routinely prepared for the Pringle maneuver and was used intermittently to keep the operative field dry when necessary. For procedures involving more extensive liver resection, such as trisectionectomy, hemihepatectomy, central bisectionectomy, and sectionectomy, we preferred the extrahepatic Glissonean approach (Figure 1), which requires the operator to predissect the Glisson system of the hemihepatic or hepatic lobe at the first hepatic portal, subsequently ligating them with vascular clips or silk wires and then severing the liver parenchyma along the ischemic line of the liver surface using an ultrasonic knife to remove the hemihepatic or hepatic lobe. In contrast, for minor liver resection, such as segmentectomy, it is difficult to use the extrahepatic Glissonean approach because the Glisson system of the hepatic segment is located deeper in the hepatic parenchyma in the hilar region. For this reason, we preferred the hepatic parenchymal transection-first approach (Figure 2), in which the surgeon predetermines the peripheral boundaries of the liver segments to be surgically removed based on anatomical landmarks or with the help of intraoperative ultrasound; then, the liver parenchyma is cut first, revealing the Glisson system of the hepatic segment during dissection, which is ligated and cut. Notably, the choice between the above two approaches is not absolute, and these approaches should be used flexibly according to the actual situation encountered intraoperatively. Lymph node dissection (LND)

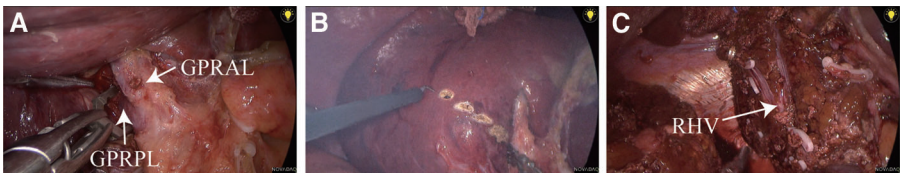

FIGURE 1
Surgical procedure for laparoscopic anatomical right posterior lobe resection (using the extrahepatic glissonean approach). (A) The Glissonean pedicle of the right posterior lobe (GPRPL) was identified, dissected free and then occluded with a bulldog clamp. (B) The extent of resection was determined according to the ischemic line, and an electrocoagulation hook was used to draw a pretransected line. (C) The right posterior lobe of the liver was removed, and the right hepatic vein trunk was preserved. GPRAL, Glissonean pedicle of right anterior lobe; GPRPL, Glissonean pedicle of right posterior lobe; RHV, right hepatic vein.

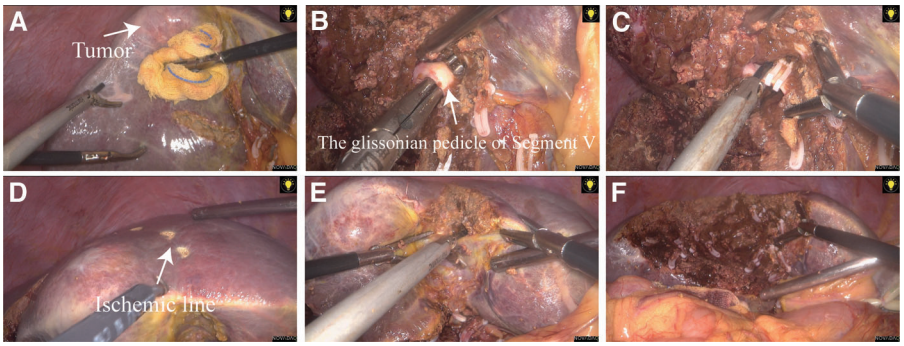

FIGURE 2
Surgical procedure for laparoscopic anatomical segment V resection (using the hepatic parenchymal transection-first approach). (A) Anatomical landmarks or intraoperative ultrasound were used to define the borders of segment V, and a pretransected line was created through ultrasonic dissection. (B) The Glissonean pedicle of segment V was dissected free during transection of the liver parenchyma. (C) The Glissonean pedicle was clamped and then cut off. (D) After inducing ischemia in segment V, we used an electrocoagulation hook to draw a pretransected line based on the ischemic line. (E) and (F) Complete transection of the remaining liver parenchyma was continued and finally, resection of segment V was completed.

in the hilar region was not routinely performed in all cases at our center; instead, this was performed only in cases in which enlarged lymph nodes were found by preoperative imaging or intraoperative observation.

Postoperative management

After surgery, all patients fasted and received intravenous nutritional support until gastrointestinal function was restored. Postoperative laboratory tests, such as the complete blood count, biochemical profile, coagulation tests, and liver function tests, were performed every two days during the postoperative recovery course. In addition, CT examination was routinely performed on the fourth postoperative day to assess the patient's intra-abdominal condition.

Data collection and definitions

We retrospectively collected data from the patient's medical records, including clinical baseline data, laboratory test results, pathological findings, intraoperative data, postoperative data, and follow-up data. Postoperative follow-up was performed once every three months by telephone. Overall survival (OS) was defined as the time from surgery until death, and recurrence-free survival (RFS) was defined as the survival duration without ICC recurrence. We used the Brisbane 2,000 classification to define the anatomical resection procedures (8). The 8th edition of the AJCC/UICC TNM staging system was applied, and perioperative complications were evaluated with the Clavien–Dindo complication classification system (9, 10).

Statistical analysis

Continuous data are presented as the mean ± standard deviation (SD) or as the median with interquartile range [median (Q1, Q3)] according to their distribution, and Student's t test or the Mann–Whitney U test was used for comparisons. Categorical data are presented as numbers with percentages (%) and were compared using the $\chi 2$ test or Fisher's exact test. OS and disease-free survival (DFS) curves were plotted following the Kaplan–Meier method, and the log-rank test was used to compare the curves. Univariate Cox regression analysis was applied to evaluate the potential risk factors for prognosis; the clinical parameters with $P < 0.10$ were entered into multiple Cox regression analysis to identify independent prognostic factors for OS or DFS. In all analyses, $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS Statistics V.25 (IBM SPSS Software) and/or R V.3.5.3.

Results

Preoperative situation

A comparison of the baseline characteristics between the OAH and LAH groups is summarized in Table 1. There were

TABLE 1 Comparison of the baseline characteristics between OAH and LAH groups.

Variables	OAH group ($n = 65$)	LAH group ($n = 30$)	P value
Age, year	61.7 ± 9.0	60.6 ± 9.4	0.616
Sex, n (%)			
Male	37 (56.9%)	11 (36.7.0%)	0.066
Female	28 (43.1%)	19 (63.3%)	
BMI, kg/m^2	23.6 ± 3.6	24.5 ± 3.7	0.292
ASA score, n (%)			
1	4 (6.2%)	4 (13.3%)	0.489[a]
2	56 (86.2%)	24 (80.0%)	
3	5 (7.7%)	2 (6.7%)	
Comorbidity, n (%)			
Diabetes	7 (10.8%)	3 (10.0%)	1.000[a]
Hypertension	19 (29.2%)	10 (33.3%)	0.686
Coronary heart disease	2 (3.1%)	3 (10.0%)	0.322[a]
History of smoking, n (%)	17 (26.2%)	10 (33.3%)	0.471
History of alcohol consumption, n (%)	21 (32.3%)	7 (23.3%)	0.373
Previous abdominal surgery, n (%)	15 (23.1%)	6 (20.0%)	0.737
Hepatitis B virus infection, n (%)	10 (15.4%)	3 (10.0%)	0.749[a]
Intrahepatic biliary lithiasis, n (%)	6 (9.2%)	5 (16.7%)	0.315[a]
Laboratory tests			
CA-199, U/ml	163.0 (16.9, 800.0)	109.6 (30.6, 1000)	0.936
AFP, U/ml	3.2 (2.1, 6.0)	3.4 (2.1, 5.6)	0.496
CEA, U/ml	4.0 (2.1, 27.4)	3.2 (2.0, 7.8)	0.223
Neutrophil count, 10^9/ml	4.5 ± 2.0	4.3 ± 1.7	0.551
Lymphocyte count, 10^9/ml	1.5 (1.3, 1.9)	1.7 (1.3, 2.2)	0.267
Platelet count, 10^9/ml	239.6 ± 88.7	241.1 ± 77.3	0.936
HGB, g/L	133.6 ± 16.3	137.5 ± 19.2	0.304
ALT, U/L	23.0 (15.0, 43.0)	19.5 (13.0, 36.0)	0.391
AST, U/L	25.0 (18.0, 39.0)	22.5 (18.0, 34.0)	0.446
TBIL, umol/L	12.8 (8.5, 27.0)	12.6 (10.3, 14.7)	0.428
ALB, g/L	41.7 ± 4.6	43.3 ± 4.0	0.084

LAH, laparoscopic anatomical hepatectomy; OAH, open anatomical hepatectomy; BMI, body mass index; ASA, American Society of Anesthesiology; CA-199, cancer antigen 19-9; AFP, alpha fetoprotein; CEA, carcinoembryonic antigen; HGB, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin. Data are presented as the mean with standard deviation ($\bar{x} \pm$ SD), or median with interquartile range [median (Q1, Q3)], or counts with percentages n (x%).
[a]Indicates using Fisher exact test.

37 males and 28 females in the OAH group, with an average age of 61.7 years, while the LAH group consisted of 11 males and 19 females, with an average age of 60.6 years; no significant differences were observed between the two groups ($P > 0.05$). There was no significant difference in body mass index (BMI) between the two groups (23.6 kg/m^2 vs. 24.5 kg/m^2, $P = 0.292$). There were also no significant differences between the two groups in sex, American Society of Anesthesiology (ASA) score, comorbidities, history of smoking, history of alcohol consumption, history of abdominal surgery, hepatitis B virus infection or intrahepatic biliary lithiasis ($P > 0.05$). The preoperative laboratory test results for tumor markers, such as CA-199, CEA, and AFP, were not significantly different between the two groups ($P > 0.05$); additionally, no significant differences were observed in the other laboratory test results ($P > 0.05$).

Pathological findings

Table 2 shows a comparison of the pathological findings between the OAH and LAH groups. The tumor diameter was clearly larger in the OAH group than in the LAH group (4.7 cm vs. 5.7 cm), but the difference was not statistically significant ($P = 0.053$). In addition, no other significant differences were found between the two groups with respect to other pathological findings, such as tumor number, pathological differentiation, TNM stage, T stage, microscopic metastatic foci, microscopic perineural invasion and microscopic microvascular invasion ($P > 0.05$).

TABLE 2 Comparison of the pathologic findings between OAH and LAH groups.

Variables	OAH group ($n = 65$)	LAH group ($n = 30$)	P value
Tumor diameter, cm	5.7 ± 0.3	4.7 ± 0.4	0.053
Tumor number, n (%)			
Single	55 (84.6%)	26 (86.7%)	1.000[a]
Multiple	10 (15.4%)	4 (13.3%)	
Pathological differentiation, *n* (%)			
Poorly differentiated	14 (21.5%)	5 (16.7%)	0.312[a]
Moderately differentiated	46 (70.8%)	25 (83.3%)	
Well differentiated	5 (7.7%)	0 (0.0%)	
TNM stage, *n* (%)			
0/IA/IB/II	38 (58.5%)	19 (63.3%)	0.652
IIIA/IIIB/IV	27 (41.5%)	11 (36.7%)	
T stage, *n* (%)			
Tis/T1a/T1b/T2	50 (58.5%)	19 (63.3%)	0.291
T3/T4	27 (41.5%)	11 (36.7%)	
Microscopic metastatic foci, *n* (%)	7 (10.8%)	6 (20.0%)	0.335[a]
Microscopic perineural invasion, *n* (%)	16 (24.6%)	9 (30.0%)	0.580
Microscopic microvascular invasion, *n* (%)	13 (20.0%)	7 (23.3%)	0.711

LAH, laparoscopic anatomical hepatectomy; OAH, open anatomical hepatectomy. Data are presented as the mean with standard deviation ($\bar{x} \pm$ SD), or counts with percentages *n* (x%).
[a]indicates using Fisher exact test. Bold indicates statistical significance.

Surgical outcomes

A comparison of the surgical outcomes between the OAH and LAH groups is shown in Table 3. The operative duration was similar in the two groups (225.3 min vs. 231.0 min, $P = 0.787$). Regarding the type of liver resection, the proportions of trisectionectomy and hemihepatectomy were higher in the OAH group than in the LAH group (3.1% vs. 0.0%, 81.5% vs. 56.7%), while the proportions of central bisectionectomy, sectionectomy, and segmentectomy were lower in the OAH group (4.6% vs. 6.7%, 4.6% vs. 30.0%, 6.2% vs. 6.7%); these differences were statistically significant ($P = 0.007$). In the LAH group, six (20.0%) patients underwent conversion to open surgery. As expected, the incision length was significantly longer in the OAH group than in the LAH group (21.1 cm vs. 11.5 cm, $P < 0.001$). Although the volume of intraoperative blood loss was significantly higher in the OAH group than in the LAH group (300.0 ml vs. 200.0 ml, $P = 0.044$), the rate of intraoperative transfusion did not differ significantly between the two groups (18.5% vs. 10.0%, $P = 0.375$). LND was performed in 37 cases (56.9%) in the OAH group and only 6 cases (20.0%) in the LAH group, and this difference was statistically significant ($P = 0.001$). Among those who underwent LND, in the OAH group, 17 (45.9%) and 20 (54.1%) patients were found to have positive and negative lymph nodes, respectively, while in the LAH group, 1 (16.7%) and 5 (83.3%) patients were found to have positive and negative lymph nodes, respectively. In addition, the patients in the OAH group were more likely to have an adequate lymph node evaluation (lymph node yield ≥6) than the patients in the LAH group (10.8% vs. 0.0%, $P = 0.001$). There were no significant differences regarding the Pringle maneuver, surgical margin, or postoperative transfusion between the two groups ($P > 0.05$). The incidence of severe complications, which were defined as those with a Clavien–Dindo grade ≥3, was higher in the OAH group than in the LAH group, but there was no significant difference (12.3% vs. 3.3%, $P > 0.05$). Furthermore, there were no significant differences between the two groups in terms of specific complications, such as incision-related complications, postoperative complications, delayed gastric emptying, bile leakage, peritoneal effusion, intraperitoneal infection, pleural effusion, lung infection, myocardial infarction, and heart failure ($P > 0.05$). One patient (1.5%) in the OAH group was transferred to the intensive care unit (ICU) because of severe

TABLE 3 Comparison of the surgical outcomes and follow-up outcomes between OAH and LAH groups.

Variables	OAH group ($n = 65$)	LAH group ($n = 30$)	*P* value
Operation *time*, min	225.3 ± 75.4	231.0 ± 103.2	0.787
Intraoperative blood loss, ml	300.0 (170.0, 275.0)	200.0 (100.0, 300.0)	**0.044**
Intraoperative transfusion, *n* (%)	12 (18.5%)	3 (10.0%)	0.375
Liver resection, *n* (%)			**0.007**[b]
Trisectionectomy	2 (3.1%)	0 (0.0%)	
Right-trisectionectomy	1 (1.5%)	0 (0.0%)	
Left-trisectionectomy	1 (1.5%)	0 (0.0%)	
Hemi-hepatectomy	53 (81.5%)	17 (56.7%)	
Right hemi-hepatectomy	14 (21.5%)	5 (16.7%)	
Left hemi-hepatectomy	39 (60.0%)	12 (40.0%)	
Central bisectionectomy	3 (4.6%)	2 (6.7%)	
Sectionectomy	3 (4.6%)	9 (30.0%)	
Left lateral sectionectomy,	1 (1.5%)	8 (26.7%)	
Right posterior sectionectomy	2 (3.1%)	1 (3.3%)	
Segmentectomy	4 (6.2%)	2 (6.7%)	
Conversion, *n* (%)	-	6 (20.0%)	-
Incision length, cm	21.1 ± 2.4	11.5 ± 5.3	**<0.001**
Intraoperative transfusions, *n* (%)	12 (18.5%)	3 (10.0%)	0.375[b]
Lymph node dissection, *n* (%)	37 (56.9%)	6 (20.0%)	**0.001**
Nodal status			
Positive	17 (45.9%)	1 (16.7%)	
Negative	20 (54.1%)	5 (83.3%)	
Lymph node yield			
0 nodes	28 (43.1%)	24 (80.0%)	**0.001**[b]
1–5 nodes	30 (46.2%)	6 (20.0%)	
≥6 nodes	7 (10.8%)	0 (0.0%)	
Pringle maneuver, *n* (%)	18 (27.7%)	10 (33.3%)	0.575
Single	15 (23.1%)	4 (13.3%)	
Multiple	3 (4.6%)	6 (20.0%)	
Surgical margin, *n* (%)			
R0	62 (95.4%)	29 (96.7%)	1.000[b]
R1	3 (4.6%)	1 (3.3%)	
Postoperative transfusion, *n* (%)	2 (3.1%)	3 (10.0%)	0.322[b]
Morbidity of complications, *n* (%)			
Clavien-Dindo ≥3	8 (12.3%)	1 (3.3%)	0.264[b]
Incision-related complications	3 (4.6%)	0 (0.0%)	0.549[b]
Postoperative haemorrhage	2 (3.1%)	1 (3.3%)	1.000[b]
Delayed gastric emptying	1 (1.5%)	0 (0.0%)	1.000[b]
Bile leakage	4 (6.2%)	1 (3.3%)	1.000[b]
Peritoneal effusion	9 (13.8%)	2 (6.7%)	0.493[b]
Intraperitoneal infection	4 (6.2%)	0 (0.0%)	0.304[b]
Pleural effusion	24 (36.9%)	9 (30.0%)	0.510
Lung infection	13 (20.0%)	1 (3.3%)	0.058[b]
Myocardial infarction	1 (1.5%)	1 (3.3%)	0.534[b]
Heart failure	3 (4.6%)	3 (10.0%)	0.376[b]
ICU admission, *n* (%)	1 (1.5%)	0 (0.0%)	1.000[b]
Postoperative hospital stays, days	10.6 ± 3.9	8.8 ± 3.3	**0.031**
Hospital cost, RMB	73597.1 ± 31001.7	75031.7 ± 21533.7	0.819
30-day death, *n* (%)	0 (0.0%)	0 (0.0%)	-
Follow-up outcomes			
Subsequent therapy, *n* (%)	16 (24.6%)	7 (23.3%)	0.892
Transarterial liver chemoembolization	6 (9.2%)	6 (20.0%)	0.186[b]
Radiofrequency ablation	4 (6.2%)	2 (6.7%)	1.000[b]
Targeted therapy	3 (4.6%)	1 (3.3%)	1.000[b]
Immunotherapy	1 (1.5%)	0 (0.0%)	1.000[b]
Reoperation	1 (1.5%)	0 (0.0%)	1.000[b]
Chemotherapy	5 (7.7%)	0 (0.0%)	0.176[b]
Radiotherapy	1 (1.1%)	0 (0.0%)	1.000[b]
Follow-up time, months[a]	13.8 (1.1, 72.2)	10.7 (1.0, 66.0)	0.731
Total disease recurrence, *n* (%)	29 (44.6%)	10 (33.3%)	0.299
Total death, *n* (%)	25 (38.5%)	9 (30.0%)	0.424

LAH, laparoscopic anatomical hepatectomy; OAH, open anatomical hepatectomy; RMB, Ren Min Bi. Data are presented as the mean with standard deviation (x ± SD), or median with interquartile range [median (Q1, Q3)], or counts with percentages *n* (x%).

[a]indicates using Fisher exact test. Bold indicates statistical significance.

[b]Data are presented as the median with range.

pulmonary infection, while no (0.0%) patients in the LAH group were transferred to the ICU ($P = 1.000$). The mean length of postoperative hospital stay was significantly longer in the OAH group than the LAH group (10.6 days vs. 8.8 days, $P = 0.031$). However, the hospital costs were similar in the two groups (73597.1 RMB vs. 75031.7 RMB, $P = 0.819$), and no deaths within 30 days after surgery were reported in either group.

Follow-up and long-term outcomes

A comparison of the follow-up and long-term outcomes between the OAH and LAH groups is shown in Table 3 and Figure 1. Sixteen patients (24.6%) in the OAH group and seven patients (23.3%) in the LAH group received subsequent therapy, with no statistically significant difference between the two groups. In addition, the two groups had similar results in terms of the use of specific subsequent therapy, such as hepatic artery chemoembolization, radiofrequency ablation,

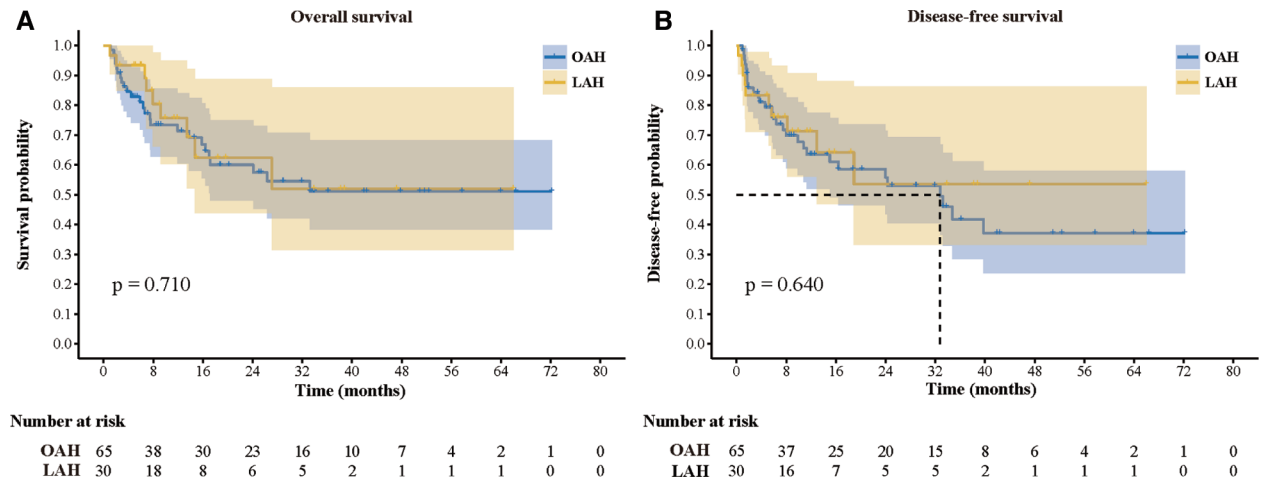

FIGURE 3
Comparison of overall survival and disease-free survival between the two groups. (A) Overall survival; (B): Disease-free survival.

targeted therapy, immunotherapy, reoperation, chemotherapy, and radiotherapy ($P > 0.05$). The median follow-up time after surgery was 13.8 (1.1, 72.2) months in the LAH group and 10.7 (1.0, 66.0) months in the OAH group ($P = 0.731$). During the follow-up period, there were 29 (44.6%) cases of recurrence and 25 (38.5) deaths in the OAH group and 10 (33.3%) cases of recurrence and 9 (30.0) deaths in the LAH group. Both the total disease recurrence rate and total mortality rate were comparable between the two groups ($P > 0.05$). The 1- and 3-year OS rates were 71.3% and 51.1% in the OAH group and 75.7% and 52.0% in the LAH group, respectively (**Figure 3A**). The 1- and 3-year DFS rates were 63.4% and 41.7% in the OAH group and 71.3% and 53.5% in the LAH group, respectively (**Figure 3B**). There was no significant difference in the OS or DFS rate between the OAH and LAH groups ($P = 0.640$ and $P = 0.710$, respectively, **Figures 3A,B**).

Univariate and multivariate analyses of factors associated with OS and DFS

The results of the univariate and multivariate analyses of variables that affect OS and DFS are shown in **Tables 4**, **5**, respectively. Multivariate analysis showed that CA-199, CEA, HGB, tumor diameter, and T stage were independent prognostic factors for OS. Of these, CA-199 (HR 1.002, 95% CI 1.001–1.003, $P = 0.001$), CEA (HR 1.009, 95% CI 1.003–1.016, $P = 0.006$), tumor diameter (HR 1.284 95% CI 1.045–1.576, $P = 0.017$), and T stage (HR 5.105, 95% CI 1.126–23.149, $P = 0.035$) were independent risk factors for OS, but HGB (HR 0.962, 95% CI 0.938–0.986, $P = 0.002$) was an independent protective factor. Additionally, multivariate analysis showed that an elevated CA-199 level (HR 1.001, 95% CI 1.000–1.002, $P = 0.018$) and T stage > T2 (HR 3.893, 95% CI 1.281–11.836, $P = 0.017$) were independent risk factors for shorter DFS.

Discussion

In the last two decades, laparoscopic hepatectomy (LH) has progressed rapidly with the development of laparoscopic techniques and the advancement of laparoscopic instruments, and laparoscopic surgery has become feasible in some complex and difficult cases in which LH was previously considered difficult. In 2002, Chen first reported LH for ICC and successfully performed LND laparoscopically (11); since then, studies on LH for ICC have emerged. In most of these studies, laparoscopic surgery has been suggested to be associated with lower morbidity rates, less pain, faster recovery, and shorter hospital stays than conventional open surgery in terms of short-term outcomes (12–15). However, none of those studies have explored the advantages and disadvantages of the two approaches in terms of short-term outcomes after anatomical hepatectomy. The present study therefore aimed to fill this gap in knowledge and identified that the intraoperative blood loss, incision length, and length of postoperative hospital stay were more favorable in the LAH group than in the OAH group. Although these findings require confirmation in larger-scale trials, they are nevertheless encouraging and indicate that the advantages of minimally invasive techniques were retained despite anatomical hepatectomy increasing the technical difficulty of laparoscopic surgery. Moreover, LAH showed encouraging results in terms of the operative duration, despite this factor

TABLE 4 Univariate and multivariate analyses of factors associated with overall survival rates.

Variable	Univariable cox regression analysis			Multivariable cox regression analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Sex male (vs. female)	1.863	0.932–3.726	0.079	2.475	0.995–6.155	0.051
Age (years)	1.041	0.999–1.084	0.056	1.030	0.981–1.081	0.232
BMI (kg/m^2)	0.932	0.852–1.021	0.130			
ASA score						
1	-	-	-			
2	1.246	0.378–4.110	0.717			
3	0.951	0.159–5.695	0.956			
Diabetes yes (vs. no)	0.555	0.133–2.317	0.419			
Hypertension yes (vs. no)	0.774	0.350–1.712	0.527			
Coronary heart disease yes (vs. no)	0.045	0.000–25.024	0.337			
History of smoking yes (vs. no)	1.151	0.550–2.408	0.709			
History of alcohol consumption yes (vs. no)	1.371	0.678–2.772	0.380			
Hepatitis B virus infection yes (vs. no)	1.278	0.529–3.089	0.585			
Intrahepatic biliary lithiasis yes (vs. no)	1.595	0.659–3.860	0.300			
CA-199 (U/ml)	1.002	1.001–1.003	**< 0.001**	1.002	1.001–1.003	**0.001**
AFP (U/ml)	1.005	0.998–1.012	0.164			
CEA (U/ml)	1.009	1.004–1.013	**0.000**	1.009	1.003–1.016	**0.006**
Neutrophil count (10^9/L)	1.252	1.085–1.444	**0.002**	1.117	0.903–1.381	0.310
Lymphocyte count (10^9/L)	0.88	0.595–1.300	0.520			
Platelet count (10^9/L)	1.002	0.998–1.006	0.371			
HGB (g/L)	0.976	0.956–0.996	**0.018**	0.962	0.938–0.986	**0.002**
ALT (U/L)	0.999	0.994–1.003	0.610			
AST (U/L)	1.007	1.000–1.014	**0.048**	1.004	0.995–1.012	0.397
TBIL (umol/L)	1.003	0.998–1.007	0.231			
ALB (g/L)	0.951	0.882–1.025	0.187			
Tumor diameter (cm)	1.189	1.047–1.351	**0.008**	1.284	1.045–1.576	**0.017**
Tumor number multiple (vs. single)	0.666	0.203–2.184	0.502			
Pathological differentiation						
Poorly differentiated	-	-	-			
Moderately differentiated	0.463	0.220–0.975	**0.043**	1.539	0.552–4.289	0.409
Well differentiated	0.207	0.026–1.628	0.135	1.909	0.163–22.309	0.606
TNM stage > II (vs. ≤ II)	2.396	1.214–4.726	**0.012**	0.147	0.019–1.148	0.067
T stage > T2 (vs. ≤T2)	2.281	1.136–4.581	**0.020**	5.105	1.126–23.149	**0.035**
Microscopic metastatic foci yes (vs. no)	3.356	1.422–7.919	**0.006**	0.950	0.296–3.047	0.931
Microscopic perineural invasion yes (vs. no)	1.733	0.797–3.770	0.166			
Microscopic microvascular invasion yes (vs. no)	1.996	0.893–4.462	0.092	2.662	0.742–9.552	0.133
Lymph node dissection yes (vs. no)	1.126	0.573–2.209	0.731			
Nodal status positive (vs. negative)	1.954	0.908–4.204	0.087	2.617	0.580–11.818	0.211
Lymph node yield						
0 nodes	-	-	-			
1–5 nodes	1.234	0.615–2.474	0.554			
≥6 nodes	0.676	0.156–2.937	0.602			
Surgical margin R1 (vs. R0)	2.539	0.770–8.375	0.126			
Subsequent therapy yes (vs. no)	0.955	0.432–2.111	0.910			
LAH (vs. OAH)	0.864	0.402–1.859	0.709			

BMI, body mass index; ASA, American Society of Anesthesiology; CA-199, cancer antigen 19-9; AFP, alpha fetoprotein; CEA, carcinoembryonic antigen; HGB, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; LAH, laparoscopic anatomical hepatectomy; OAH, open anatomical hepatectomy. Bold indicates statistical significance.

TABLE 5 Univariate and multivariate analyses of factors associated with disease-free survival rates.

Variable	Univariable cox regression analysis			Multivariable cox regression analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Sex male (vs. female)	1.408	0.747–2.653	0.290			
Age (years)	1.001	0.968–1.037	0.933			
BMI (kg/m^2)	1.008	0.96–1.059	0.738			
ASA score						
1	-	-	-			
2	1.080	0.380–3.068	0.885			
3	1.050	0.234–4.708	0.950			
Diabetes yes (vs. no)	0.199	0.027–1.455	0.112			
Hypertension yes (vs. no)	0.504	0.222–1.143	0.101			
Coronary heart disease yes (vs. no)	0.044	0.000–10.635	0.265			
History of smoking yes (vs. no)	0.816	0.387–1.720	0.593			
History of alcohol consumption yes (vs. no)	0.941	0.468–1.892	0.865			
Hepatitis B virus infection yes (vs. no)	1.621	0.745–3.529	0.223			
Intrahepatic biliary lithiasis yes (vs. no)	1.893	0.834–4.297	0.127			
CA-199 (U/ml)	1.001	1.000–1.002	**0.003**	1.001	1.000–1.002	**0.018**
AFP (U/ml)	1.003	0.997–1.010	0.317			
CEA (U/ml)	1.003	0.998–1.009	0.247			
Neutrophil count (10^9/L)	1.239	1.083–1.416	**0.002**	1.180	0.984–1.416	0.074
Lymphocyte count (10^9/L)	0.943	0.805–1.103	0.463			
Platelet count (10^9/L)	1.004	1.000–1.008	0.061	1.004	0.999–1.008	0.100
HGB (g/L)	0.986	0.966–1.006	0.178			
ALT (U/L)	1.000	0.997–1.003	0.809			
AST (U/L)	1.006	0.999–1.013	0.080	0.999	0.991–1.007	0.815
TBIL (umol/L)	1.002	0.998–1.007	0.269			
ALB (g/L)	0.962	0.897–1.031	0.273			
Tumor diameter (cm)	1.182	1.047–1.334	**0.007**	1.126	0.961–1.320	0.143
Tumor number multiple (vs. single)	0.669	0.237–1.886	0.447			
Pathological differentiation						
Poorly differentiated	-	-	-			
Moderately differentiated	0.599	0.289–1.240	0.167			
Well differentiated	0.495	0.107–2.291	0.368			
TNM stage >II (vs. ≤II)	2.878	1.521–5.446	**0.001**	0.753	0.235–2.411	0.633
T stage >T2 (vs. ≤T2)	3.581	1.851–6.925	**< 0.001**	3.893	1.281–11.836	**0.017**
Microscopic metastatic foci yes (vs. no)	1.538	0.587–4.028	0.381			
Microscopic perineural invasion yes (vs. no)	1.522	0.706–3.283	0.284			
Microscopic microvascular invasion yes (vs. no)	2.153	1.024–4.525	**0.043**	1.761	0.686–4.519	0.239
Lymph node dissection yes (vs. no)	1.083	0.578–2.031	0.803			
Nodal status positive (vs. negative)	1.605	0.758–3.400	0.216			
Lymph node yield						
0 nodes	-	-	-			
1–5 nodes	1.145	0.593–2.211	0.688			
≥6 nodes	0.842	0.249–2.841	0.781			
Surgical margin R1 (vs. R0)	1.598	0.383–6.667	0.520			
Subsequent therapy yes (vs. no)	1.546	0.793–3.015	0.201			
LAH (vs. OAH)	0.841	0.409–1.729	0.637			

BMI, body mass index; ASA, American Society of Anesthesiology; CA-199, cancer antigen 19-9; AFP, alpha fetoprotein; CEA, carcinoembryonic antigen; HGB, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; LAH, laparoscopic anatomical hepatectomy; OAH, open anatomical hepatectomy. Bold indicates statistical significance.

being reported as a disadvantage of laparoscopic surgery in previous studies (16). In our study, although the operative duration was slightly longer in the LAH group than the OAH group, the difference was not statistically significant. We believe that this is because the surgeons had already accumulated sufficient experience to overcome the learning curve of LH, as they performed a large number of LH surgeries at our center. In this study, the proportions of trisectionectomy and hemihepatectomy in the LAH group were significantly lower than those in the OAH group, while the proportions of central bisectionectomy, sectionectomy and segmentectomy in the LAH group were significantly higher than those in the OAH group. These findings suggest that LAH was likely to enable the resection of a lower volume of liver tissue, which was also found in previous studies (14, 17). We think that this phenomenon can be explained by the clear but not statistically significant difference in tumor diameter between the two groups in our study. The tumor diameter was much larger in the OAH group, which inevitably led to the need for more extensive resection. Nonetheless, this finding also indicates the possibility of patient selection bias, which is one of the limitations of this study. In terms of postoperative complications, Hobeika et al. studied 548 ICC patients who underwent laparoscopic and open surgery and found that the incidence of overall complications and severe complications was lower in the laparoscopic group than in the open group but that the difference was not significant; this trend has been observed in most of the previous studies (15, 16). Similarly, our study also found a downward trend in the incidence of complications in the LAH group, including grade 3 or 4 complications, incision-related complications, postoperative hemorrhage, and delayed gastric emptying, among others, but again, with no significant differences.

There is still controversy over the need for routine LND in patients with ICC. Some opponents argue that LND is not beneficial for ICC patients because LND fails to improve OS or DFS in such patients and instead leads to an increase in postoperative complications (15, 16, 18, 19). However, proponents argue that routine LND in ICC patients is beneficial, as they believe that LND not only prolongs OS and DFS but also allows for accurate lymph node staging, which can help in determining the patient's prognosis and developing subsequent adjuvant treatment plans (20, 21). Although there is a consensus among some current recommendations that routine LND should be performed in patients with ICC, there is still a gap between current clinical practice and these guidelines. Our study also points to another important issue: the LND rate was lower in the LAH group than in the OAH group. This is not a coincidental finding and has been mentioned in several previous studies. Hobika et al. found a lower probability of LND in the laparoscopic group than in the open group in a nationwide study (12). In addition, Martin et al. suggested that laparoscopic treatment for ICC was associated with worse lymph node evaluations than open surgery (22), while several other meta-analyses also concluded that the LND rate was lower in the laparoscopic group (23, 24). We believe that the main reasons for this are the high degree of technical difficulty in performing LND laparoscopically and the lack of a consensus on the use of routine LND in clinical practice, which leads to a preference for not performing LND when left to the discretion of the laparoscopic surgeon. Reassuringly, this divide seems to have improved in recent years with the advancement of laparoscopic techniques and the development of laparoscopic instruments. In a recent single-center study, Ratti et al. demonstrated that laparoscopic liver resection (LLR) can achieve a higher percentage of complete LND and fewer LND-related complications (25). Moreover, the da Vinci surgical platform, which has become more widely used in recent years, provides an expanded three-dimensional view and greater degrees of freedom through the articulating arms, and we have reason to believe that this tool will make LND even easier.

The lack of haptic feedback is one of the main disadvantages of laparoscopic surgery in clinical practice because it may preclude surgeons from accurately judging the location of certain portions of the tumor boundary. This can lead to an increased rate of positive surgical margins during the operation and inevitably result in a poorer prognosis. Theoretically, *en bloc* resection, avoiding a positive surgical margin and any residual tumor, reduces tumor growth and metastasis and therefore results in better OS and DFS; this view has been demonstrated in previous studies (26, 27). However, in the current study, we did not find any association between surgical margin and OS or DFS on either univariate or multivariate regression analysis, which we speculate may result from the bias related to the small sample size. Reassuringly, similar surgical margin outcomes were achieved in the two groups, indicating that LAH could reach the same oncologic adequacy as OAH. We suspect that this could be due to the surgeon's skill level and advantages of anatomical hepatectomy in achieving oncologic adequacy, which compensated for the deficiencies in haptic feedback. In the present study, similar OS and DFS rates were achieved in the LAH and OAH groups, which is consistent with the findings of most previous reports (14, 15, 23, 24). Additionally, both the total disease recurrence rate and total mortality rate were comparable between the two groups. This strongly suggests that compared with OAH, LAH can achieve similar long-term outcomes and is a safe and feasible alternative treatment for ICC patients.

This study has several limitations. First, this study was not a randomized controlled trial, so patient selection bias may be present. Second, this was a single-center study, and we further screened the sample to include patients undergoing anatomical resection, which resulted in a small sample size

and further resulted in insufficient statistical power. Therefore, there is a need for future large-sample, multicenter, and high-quality interventional studies comparing LAH with OAH in ICC. Finally, the data on subsequent therapy, recurrence and mortality in this study relied on the retrospective recall of the patients or their families, which may have resulted in recall bias. Moreover, some parameters of the subsequent therapeutic strategies, such as number of cycles, regimen, dose, etc., were not listed; only whether the patient received some kind of subsequent therapy was recorded, thereby leading to a limited interpretation of each patient's prognostic outcome.

Conclusion

In conclusion, LAH for ICC is safe and feasible when performed by experienced surgeons. Furthermore, our study revealed that LAH provides better short-term outcomes than OAH and leads to a comparable long-term prognosis.

Data availability statement

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

Ethics statement

Ethical review and approval was obtained from the Ethics Committee of Qilu Hospital, Shandong University (approval number: KYLL-202011-180). Written informed consent from the patients was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication. 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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Orthopedic therapeutic surgery for bone metastasis of liver cancer: Clinical efficacy and prognostic factors

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Objectives: In this study, the objectives were to investigate the clinical efficacy of orthopedic therapeutic surgery (OTS) in patients with bone metastasis of liver cancer and explore the prognostic factors.

Methods: The electronic medical records of patients with bone metastasis of liver cancer in the Third Affiliated Hospital of Naval Medical University from September 2016 to August 2021 were retrospectively collected. A total of 53 patients were included. Patients were assigned to the OTS ($n = 35$) or the control group ($n = 18$) based on receiving orthopedic therapeutic surgery or conservative treatment. The pre/posttreatment Karnofsky Performance Status scale (KPS) and numeric rating scale (NRS) scores were compared. Univariate and multivariate Cox regression analyses were used to explore the prognostic factors affecting survival after bone metastasis. Logistic regression analyses were adopted to discover potential factors that contributed to greater KPS score improvement.

Results: The axial bone accounted for 69.8% of all bone metastases. The proportion of multiple bone metastases was 52.8%. After surgery, the median KPS score of the OTS group increased from 60 to 80 ($p < 0.001$), and the median increase in the OTS group was higher than that of the control group ($p = 0.033$). The median NRS score of the OTS group declined from 6 to 2 after surgery ($p < 0.001$), and the median decline in the OTS group was higher ($p = 0.001$). The median survival was 10 months in the OTS group vs. 6 months in the control group ($p < 0.001$). Higher pretreatment KPS scores, undergoing liver primary lesion surgery, and undergoing orthopedic therapeutic surgery were protective factors of survival. Undergoing orthopedic therapeutic surgery greatly improved the KPS score.

Conclusions: Orthopedic therapeutic surgery for bone metastasis of liver cancer provides benefits to the quality of life. Patients who have their primary liver lesions removed, undergo orthopedic therapeutic surgery, and have a better physical condition before treatment tend to have longer survival.

KEYWORDS

liver neoplasms, bone metastasis, orthopedic surgery, quality of life, prognostic factors, survival

Introduction

Liver cancer, including hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and combined hepatocellular–cholangiocarcinoma (CHC), is one of the most common malignant neoplasms in Asia (1, 2). The most recent 2018 data indicated that the age-standardized incidence rates of liver cancer in China and South Korea were above 15 per 100,000 (1). HCC accounts for more than 90% of liver cancer (2). Previously, the survival time of HCC patients was short and the symptoms of bone metastasis were rarely reported due to the poor control of the primary lesions (3). Recently, with the development of the therapy strategy, the survival time of liver cancer patients has been prolonged. Correspondingly, a higher diagnostic rate of liver cancer bone metastasis attracts more attention. In recent reports, bone has become the second most common metastatic site of HCC, accounting for 25% of extrahepatic metastases of HCC (4–6). The existence of bone metastasis can cause pain, pathological fractures, paralysis, and other skeletal-related events, which seriously affect patients' quality of life.

Studies have revealed that radiotherapy for bone metastasis of liver cancer brings certain therapeutic benefits (7–11). However, radiotherapy cannot maintain and restore bone stability, which may lead to pathological fractures. In addition, there are risks of radiation resistance and nontarget damage to important adjacent structures (e.g., spinal cord and bone marrow) (12–14). The new concept holds that if there are only limited bone metastases sites, especially for patients whose primary tumor has been radically resected, resection of bone lesions is expected to cure the tumor and improve patients' survival rate. In this situation, *en bloc* resection and reconstruction of the metastatic sites should be performed following the principles of primary malignant bone tumor surgery (15). For patients with better physical conditions, especially those with a longer expected survival time and limited bone metastases, surgery can eliminate the lesions to the greatest extent and provide immediate bone stability, which may benefit patients more.

To our knowledge, no previous research focused on surgical treatment for bone metastasis of liver cancer. As the main partner hospital of the China National Center for Liver Cancer, the Third Affiliated Hospital of Naval Medical University (Eastern Hepatobiliary Surgery Hospital) has treated a large number of liver cancer patients, many of whom have developed bone metastasis. Herein, we retrospectively analyzed the clinical information of patients with bone metastasis of liver cancer treated in our hospital and explored the potential factors that affect patients' survival and quality of life.

Patients and methods

Patients

This retrospective study was approved by the Ethics Committee of the Third Affiliated Hospital of Naval Medical University (Second Military Medical University). This study was conducted in accordance with the principle of the Helsinki Declaration. Written informed consent to participate in this study was obtained from all patients.

The electronic medical record system of the Third Affiliated Hospital of Naval Medical University (Eastern Hepatobiliary Surgery Hospital) was searched retrospectively. Patients whose primary diagnosis contained the expected keywords (i.e., "malignant tumor," "metastasis," "occupying lesion," "pathological fracture," and "compression fracture") were collected. In total, 154 patients were preliminarily selected. Furthermore, we reviewed their medical records and excluded unwanted data according to the inclusion and exclusion criteria. All cases of primary liver cancer were assessed, regardless of the histology and treatment of the primary liver lesion. Eventually, 53 patients were enrolled in this research. The last follow-up date was March 1, 2022. One patient lost to follow-up 6 months after the diagnosis of bone metastasis. Five patients survived at the end of the follow-up.

To eliminate possible biases, we carefully designed the inclusion and exclusion criteria. The inclusion criteria for this study were as follows: (1) Bone metastasis was diagnosed between September 2016 and August 2021; (2) The primary tumor was pathologically diagnosed as liver cancer, or the bone lesion was pathologically confirmed as the origin of liver cancer; (3) Patients received surgical or conservative treatment in our hospital; (4) Patients were assessed as Child–Pugh class A or B when diagnosed with bone metastasis; (5) The expected survival time was more than 3 months after diagnosis of bone metastasis.

The exclusion criteria for this study were as follows: (1) Existence of extra-osseous distant metastasis; (2) The bone lesions received radiotherapy; (3) Responsible bone metastasis lesions that cause symptoms were unresectable; (4) Patients who had other medical conditions that might affect their life expectancy; (5) Patients who had primary neurological disorders that might affect postoperative function; (6) Existence of portal vein tumor embolus.

Group and treatment choices

For each patient, a variety of imaging examinations, including ultrasound, x-ray, enhanced CT and MRI, and PET/CT, were applied to confirm the sites and number of bone

metastasis and to help exclude metastases in other organs. Blood tests such as liver and kidney function, electrolytes, coagulation function, and tumor markers were also routinely used to assist in evaluating the basic condition of patients. The biopsy of bone metastases was not required for all patients.

To explore the different outcomes between orthopedic therapeutic surgery (OTS) and conservative treatment, we divided 53 patients into the OTS group and the control group. Orthopedic therapeutic surgery includes radical and palliative surgery, and excludes diagnostic surgery. The common radical surgery includes artificial tumor prosthesis replacement and *en bloc* resection. The common palliative surgery includes intralesional resection (with or without internal fixation), percutaneous vertebroplasty, percutaneous kyphoplasty, or a combination (**Figures 1**, **2**).

The decision of performing orthopedic therapeutic surgery was made by comprehensively considering the patient's local condition of bone metastases, the degree of pain, the risk of pathological fracture, the physical condition, the life expectancy, and the patient's willingness. The surgery was performed by experienced surgeons. The orthopedic-related conservative (nonsurgical) treatment included physiotherapy, bisphosphonates, and pain-relief medication such as nonsteroidal anti-inflammatory drugs and opioids. For patients who did not meet the surgery criteria or refused surgery, orthopedic conservative treatment was exerted. At the same time, chemotherapy, radiotherapy, targeted therapy, and immunotherapy were performed selectively according to the treatment plan of the Hepatobiliary Department.

Physical therapy was started early after surgery to prevent complications such as venous thrombosis and hypostatic pneumonia. Systematic rehabilitation exercises were carried out in the hospital or at home under the guidance of a doctor.

The assessment of physical condition and pain level

The Karnofsky Performance Status scale (KPS) score was utilized to evaluate the patient's physical condition and functional impairment. A higher KPS score meant better physical condition and less functional impairment (16). The numeric rating scale (NRS) score was adopted to grade the patient's degree of pain. A lower NRS score meant less pain (17). These two scores were determined before treatment and 1 month after treatment. The changes were scrutinized to measure the improvement in the patient's quality of life.

Statistical analysis

For the measurement data conforming to the normal distribution, mean ± standard deviation was used, and the Student's *t*-test was applied for comparison. For the measurement data that did not conform to the normal distribution, the median (range) was utilized to display, and the Mann–Whitney *u*-test was applied for comparison. The Chi-square test or Pearson test was performed for comparison of counting data.

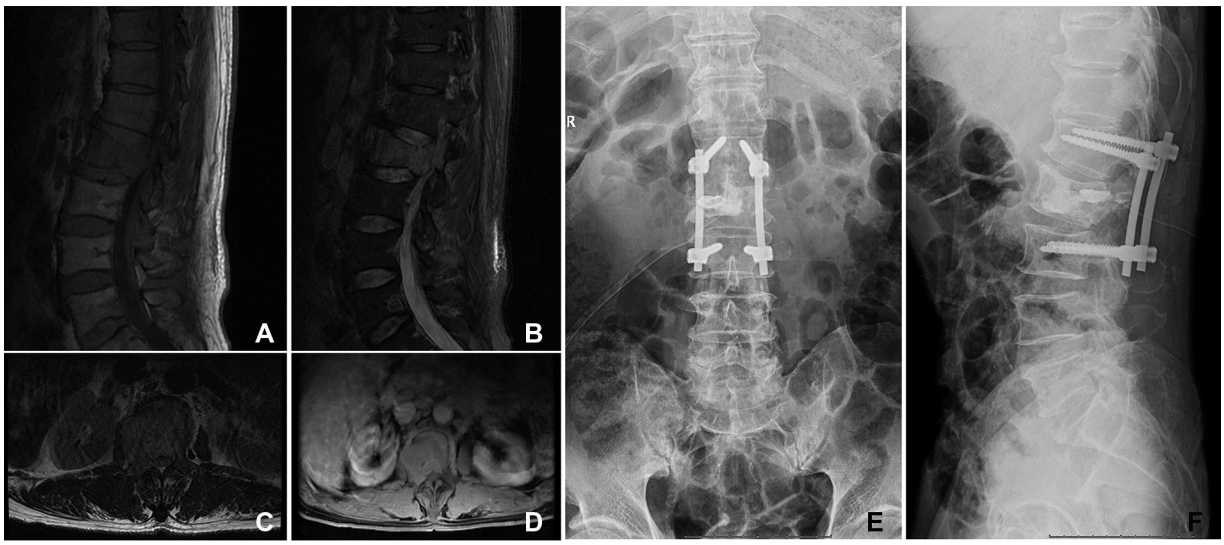

FIGURE 1
A 66-year-old woman suffered from HCC with multiple metastases of the spine and pelvis. The primary lesion of the liver was not resected. The symptoms were located in the lumbar 2 vertebra. She underwent orthopedic therapeutic surgery. (**A–D**) The L2 vertebral metastases in MRI. (**E**,**F**) The patient received intralesional resection with internal fixation and PKP. PKP, percutaneous kyphoplasty.

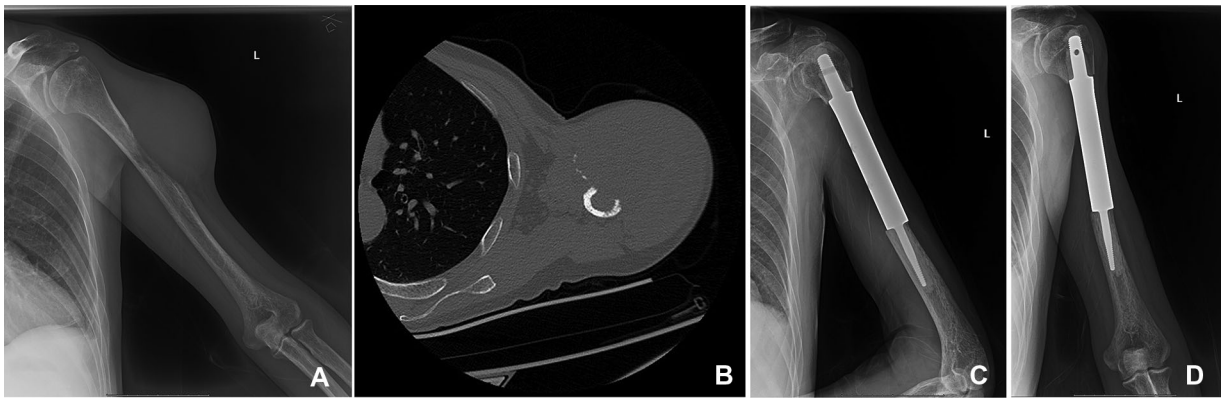

FIGURE 2
A 50-year-old man suffered from HCC with metastasis of the left humerus. The primary lesion of the liver was resected. (A,B) The bone metastasis in the middle part of the left humerus in x-ray and CT. (C,D) The patient underwent segmental tumor resection and artificial tumor prosthesis reconstruction.

The median (range) of pre/posttreatment KPS and NRS were calculated. The pre/posttreatment KPS scores in the OTS group or control group were compared, respectively, using the Mann–Whitney *u*-test, so did the comparison of posttreatment KPS scores between OTS and the control group. The same statistical method was performed in comparison of the NRS scores.

The univariate and multivariate Cox regression was used to explore the potential risk factors of survival time after bone metastasis. Disease-related death during follow-up was defined as the primary outcome. For categorical variables, the Kaplan–Meier method and log-rank test were applied to preliminarily probe risk factors. For continuous variables, the univariate Cox regression analysis was applied to initially explore possible prognostic factors. The variables whose *p*-value was under 0.2 were enrolled in multivariate Cox regression analysis, and a stepwise procedure was executed to correct confounding variables. To note, the variables that had a potential collinear relationship were omitted.

The univariate and multivariate logistic regression was exploited to discover potential influence factors of greater KPS score improvement (i.e., posttreatment KPS score minus pretreatment KPS score was greater than or equal to 20). The greater KPS score improvement was defined as the outcome. The univariate logistic regression analysis was exploited to initially explore possible influence factors. The variables whose *p*-value was under 0.2 were accepted in multivariate logistic regression analysis, and a stepwise procedure was performed to correct confounding variables. The same, the variables that had a potential collinear relationship were ruled out.

All statistical analyses were processed using IBM SPSS Statistics 25.0, and $p < 0.05$ was considered statistically significant.

Results

Patients' clinical characteristics

A total of 53 patients were enrolled in the cohort. Patients' baseline data were exhibited in Table 1. Among them, 35 patients (66%) underwent orthopedic therapeutic surgery and 18 patients received conservative treatment. Men were the majority in both the OTS group and the control group (74.3% and 83.3%, respectively). The majority of patients were diagnosed with HCC (73.6% in the whole cohort) by the pathological examination, and no one was diagnosed with CHC. For the OTS group, only two patients underwent radical surgery and the remaining 33 patients received palliative surgery. The median follow-up duration was 8 months (range 2–30). The anatomical distribution of bone metastasis was listed in Table 2.

The OTS group and the control group were compared in gender, age, pathological type, multiple bone metastases, sites of bone metastasis, pretreatment KPS score, α-fetoprotein (AFP), AFP-L3, and PIVKA. The differences were not statistically significant. It is worth noting that there were statistically significant differences between the two groups in liver primary lesion surgery, pathological fractures, and pretreatment NRS scores. In the OTS group, there was a higher proportion of patients who underwent surgery on the liver primary lesion or suffered pathological fractures, and a higher pretreatment NRS score. These results suggested that these factors may increase the willingness of patients to receive orthopedic therapeutic surgery.

TABLE 1 Clinical characteristics of patients with bone metastasis of liver cancer.

	n (%) or mean ± SD or median (range)			*p*-value
	OTS group (*n* = 35)	Control group (*n* = 18)	Total	
Male/female	26 (74.3)/9 (25.7)	15 (83.3)/3 (16.7)	41 (77.4)/12 (22.6)	0.730
Age (years)	60.2 ± 10.2	62.4 ± 10.0	60.9 ± 10.1	0.460
Pathological type				0.191
HCC	28 (80.0)	11 (61.1)	39 (73.6)	
ICC	7 (20.0)	7 (38.9)	14 (26.4)	
Liver primary lesion surgery	27 (77.1)/8 (22.9)	3 (16.7)/15 (83.3)	30 (56.6)/23 (43.4)	<0.001*
Multiple bone metastases	18 (51.4)/17 (48.6)	10 (55.6)/8 (44.4)	28 (52.8)/25 (47.2)	0.776
Sites of bone metastasis				0.328
Axial bones only	26 (74.3)	11 (61.1)	37 (69.8)	
Appendicular bones only	5 (14.3)	2 (11.1)	7 (13.2)	
Mixed	4 (11.4)	5 (27.8)	9 (17.0)	
Pathological fracture	14 (40.0)/21 (60.0)	2 (11.1)/16 (88.9)	16 (30.2)/37 (69.8)	0.030*
Pretreatment KPS score[a]	60 (30–70)	60 (50– 80)	60 (30–80)	0.403
Pretreatment NRS score[a]	6 (4–10)	5 (4–6)	6 (4–10)	<0.001*
AFP positive	13 (37.1)/22 (62.9)	5 (27.8)/13 (72.2)	18 (34.0)/35 (66.0)	0.495
AFP-L3 positive	14 (40.0)/21 (60.0)	4 (22.2)/14 (77.8)	18 (34.0)/35 (66.0)	0.196
PIVKA positive	15 (42.9)//20 (57.1)	6 (33.3)/12 (66.7)	21 (39.6)/32 (60.4)	0.502

OTS, orthopedic therapeutic surgery; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; KPS, Karnofsky Performance Status scale; NRS, numeric rating scale; AFP positive, AFP level ≥20 ng/ml; AFP-L3 positive, AFP-L3 percentage ≥10%; PIVKA positive, PIVKA level >40 mAU/ml.
[a]Expressed as median (range).
*p-value < 0.05.

TABLE 2 Distribution of bone metastasis sites.

Sites of bone metastasis	OTS group	Control group	Total
Axial bones only	26	11	37
Thoracic vertebra	5	2	7
Lumbar vertebra	8	3	11
Sacral vertebra	1	1	2
Rib	1	/	1
Multiple axial bones[a]	11	5	16
Appendicular bones only	5	2	7
Humerus	1	/	1
Radius	1	/	1
Ilium	/	1	1
Femur	1	1	2
Multiple appendicular bones[a]	2	/	2
Mixed[b]	4	5	9

OTS, orthopedic therapeutic surgery.
[a]Multiple metastases at one anatomical site were categorized as "multiple axial bones" or "multiple appendicular bones" (e.g., one patient with several lumbar metastases was categorized as "multiple axial bones").
[b]Multiple metastases occurred in both axial bones and appendicular bones.

The benefit of orthopedic therapeutic surgery

The KPS and NRS scores before and one month after treatment were evaluated respectively. The scores pre/posttreatment within or between groups were compared to investigate whether orthopedic therapeutic surgery had an association with better quality of life and pain relief.

As shown in Figure 3, although the median posttreatment KPS score was higher than the median pretreatment KPS score in the control group (70 vs. 60), it was not statistically significant ($p = 0.104$). The median KPS score of the OTS group increased from 60 (range 30–70) before OTS to 80 (range 30–90) after OTS ($p < 0.001$). Additionally, the median increase in posttreatment KPS score of the OTS group was higher than that of the control group (20 vs. 10), which was statistically significant ($p = 0.033$).

As Figure 4 exhibited, the median NRS score of the OTS group declined from 6 (range 4–10) pretreatment to 2 (range 0–4) one month after treatment ($p < 0.001$). Comparatively, the median NRS score of the control group declined from 5 (range 4–6) before treatment to 3 (range 1–5) after treatment ($p < 0.001$). Moreover, the median decline in posttreatment NRS

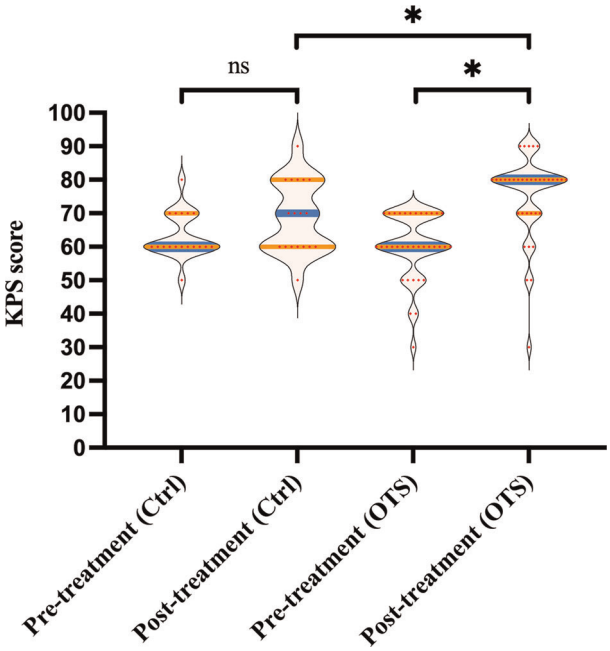

FIGURE 3
The KPS score pre/posttreatment.

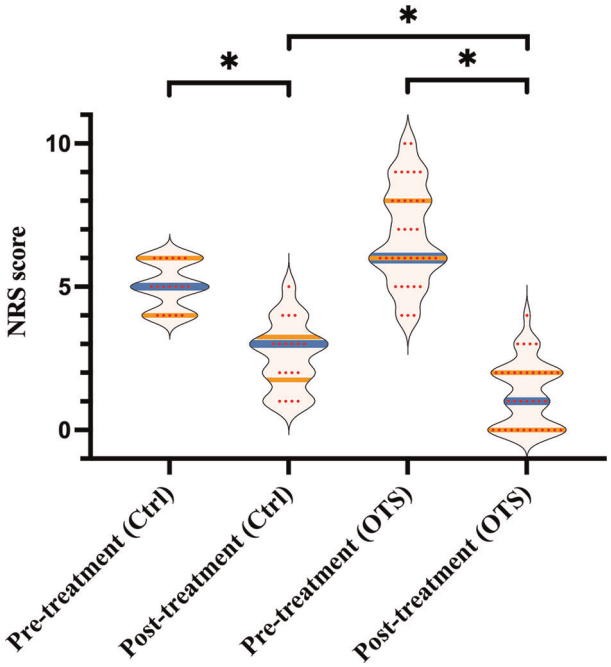

FIGURE 4
The NRS score pre/posttreatment.

score of the OTS group was more than that of the control group (4 vs. 2), which was also statistically significant ($p = 0.001$).

These data indicated that orthopedic therapeutic surgery improved postoperative functional status and achieved greater pain relief in patients compared with conservative treatment.

The impact of orthopedic therapeutic surgery on survival time

To further explore the prognostic factors of survival time after bone metastasis, the Cox regression analysis was performed. The median survival time of all patients was 9 months (range 2–30). The survival curves of the OTS group and the control group were drawn by the Kaplan–Meier method (Figure 5). The median survival time of the patients of the OTS group was 10 months (range 2–30) and that of the control group was 6 months (range 3–10). The difference was statistically significant ($p < 0.001$). These results were further investigated in subsequent multivariate Cox regression analysis.

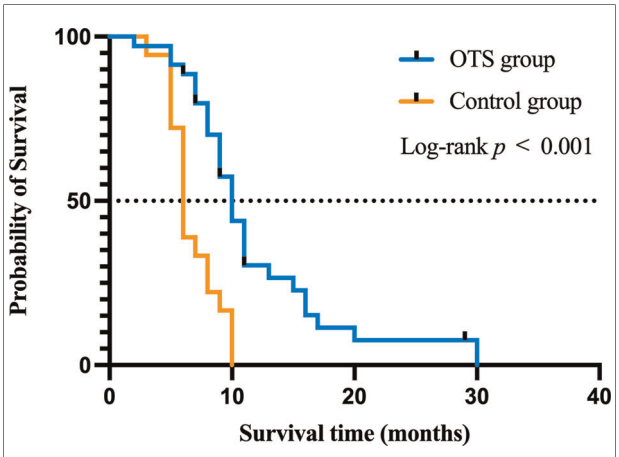

FIGURE 5
The impact of orthopedic therapeutic surgery and conservative treatment on the survival of patients after bone metastasis.

The prognostic factors of survival time of patients with bone metastasis of liver cancer

To explore the prognostic factors affecting the survival time of patients with bone metastasis of liver cancer and correct for confounding factors, a Cox regression analysis of the clinical data of all patients ($n = 53$) was performed (Table 3).

The univariate Cox analysis showed that liver primary lesion surgery, orthopedic therapeutic surgery, number of bone metastasis, sites of bone metastasis, and pretreatment KPS score had statistical significance on the survival time after bone metastasis.

TABLE 3 Cox regression analysis to identify the prognostic factors of survival time.

Variables	Univariate analysis *p*-value	Multivariate analysis	
		HR (95% CI)	*p*-value
Sex	0.796		
Age	0.221		
Pathological type[b] (HCC = 1, ICC = 2)	0.155	—	—
Liver primary lesion surgery[b]	<0.001*	0.243 (0.110–0.540)	0.001*
Multiple bone metastases[b]	0.081	—	—
Number of bone metastasis[a]	0.009*		
Sites of bone metastasis[a]	0.024*		
Pathological fracture	0.784		
Orthopedic therapeutic surgery[b]	<0.001*	0.135 (0.145–0.687)	0.004*
Pretreatment KPS score[b]	0.007*	0.917 (0.879–0.956)	<0.001*
Pretreatment NRS score	0.555		
AFP positive[b]	0.164	—	—
AFP-L3 positive	0.230		
PIVKA positive	0.791		

HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; KPS, Karnofsky Performance Status scale; NRS, numeric rating scale; AFP positive, AFP level ≥20 ng/ml; AFP-L3 positive, AFP-L3 percentage ≥10%; PIVKA positive, PIVKA level >40 mAU/ml.
[a]Due to collinearity with "Multiple bone metastases," it was not included in the multivariate Cox regression analysis.
[b]Included in the multivariate Cox regression analysis.
*p-value < 0.05.

Pathological type, liver primary lesion surgery, multiple bone metastases, orthopedic therapeutic surgery, pretreatment KPS score, and AFP positive were further enrolled in the multivariate Cox analysis to correct for confounding factors. (Number of bone metastasis and sites of bone metastasis was excluded due to the collinearity with "Multiple bone metastases"). The final result indicated that a higher pretreatment KPS score, undergoing liver primary lesion surgery, and undergoing orthopedic therapeutic surgery were protective factors, and the differences were statistically significant.

The influence factors of greater KPS score improvement in patients with bone metastasis of liver cancer

Since the basic physical conditions of advanced cancer patients were important (evaluated by KPS scores), we further explored the potential influence factors of greater KPS score improvement (Table 4).

TABLE 4 The logistic regression to identify the influence factors of greater KPS score improvement.

Variables	Univariate analysis *p*-value	Multivariate analysis	
		OR (95% CI)	*p*-value
Sex	0.749		
Age	0.668		
Pathological type (HCC = 1, ICC = 2)	0.410		
Liver primary lesion surgery[b]	0.003*	—	—
Number of bone metastasis[b]	0.099	—	—
Sites of bone metastasis[a]	0.134		
Pathological fracture	0.553		
Orthopedic therapeutic surgery[b]	0.009*	8.718 (2.214–35.783)	0.003*
Pretreatment KPS score	0.818		
Pretreatment NRS score	0.319		
AFP positive[b]	0.095	—	—
AFP-L3 positive	0.283		
PIVKA positive	0.592		

Greater KPS score improvement (posttreatment KPS score minus pretreatment KPS score was greater than or equal to 20) was defined as the outcome.
OR, odds ratio; CI, confidence interval; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; KPS, Karnofsky Performance Status scale; NRS, Numeric rating scale; AFP positive, AFP level ≥20 ng/ml; AFP-L3 positive, AFP-L3 percentage ≥10%; PIVKA positive, PIVKA level >40 mAU/ml.
[a]Due to collinearity with "Number of bone metastasis", it was not included in the multivariate logistic regression analysis.
[b]Included in the multivariate logistic regression analysis.
*p-value < 0.05.

The univariate logistic regression analysis showed that liver primary lesion surgery and orthopedic therapeutic surgery had statistical significance on the greater KPS score improvement.

Liver primary lesion surgery, orthopedic therapeutic surgery, number of bone metastasis, and AFP positive were further enrolled in the multivariate logistic analysis to correct for confounding factors ("Sites of bone metastasis" was excluded due to the collinearity with "Number of bone metastasis"). The final result indicated that undergoing orthopedic therapeutic surgery was the positive factor that contributed to a greater KPS score improvement and was statistically significant ($p = 0.003$).

Discussion

Liver cancer is the second most common cause of cancer mortality in the Asia-Pacific region (2), and the incidence of liver cancer is much higher in Asia than in Europe and the Americas, with HBV and other infections being the main risk

factors (1, 2, 18). As mentioned above, attributing to advances in diagnosis and treatment, more bone metastases are diagnosed and concerned.

In the study by Si et al., bone metastasis occurred in 9.8% of all HCC patients (34/347) (19). To note, bone metastasis may occur even after the radical resection of the primary tumor (20, 21). The spine is reported to be the most common site of bone metastasis, and about 70% of patients with bone metastases are multiple (6). Previous literature has explored the efficacy of radiotherapy on bone metastasis of liver cancer (8–11). However, for patients with a longer expected survival time, or those whose primary lesions are controlled while the symptoms of bone metastasis are severe, surgery has multiple advantages such as reducing tumor burden, maintaining bone stability, and preventing long-term bone-related complications. Taking advantage of the great number of liver cancer patients in our hospital, this study probed the impact of surgical treatment for bone metastasis of liver cancer and potential prognostic factors of survival time after bone metastasis. As far as we know, there is no previous literature on surgical treatment for bone metastasis of liver cancer.

In this study, the clinical characteristics of all patients were analyzed. In the current cohort, there were more men than women and HCC was predominant, which is consistent with epidemiology (1, 2). Several variables were found to be statistically significant between the OTS and control groups, including liver primary lesion surgery, pathological fractures, and pretreatment NRS score. We infer that patients with these factors were more willing to undergo orthopedic therapeutic surgery for bone metastasis. For patients whose primary liver tumor has been resected, if symptomatic bone metastases have a chance of being resolved, they would more actively seek help from an orthopedic surgeon for better survival. Patients with pathological fractures, or patients with severe pain, on the premise of a long-expected survival time, would be more willing to relieve pain and recover function through orthopedic therapeutic surgery.

We further confirmed that orthopedic therapeutic surgery for bone metastasis improved the quality of life and prolonged the survival time. Univariate and multivariate regression analyses also verified the positive effect of orthopedic therapeutic surgery on bone metastasis in prolonging the survival time and improving KPS scores after bone metastasis. In addition, patients in this study whose primary liver lesions were resected and who were in relatively good physical and functional status pretreatment may have longer survival.

We revealed that active intervention on bone metastasis might help improve the quality of life, which is consistent with some known literature (3, 4). However, it is worth mentioning that liver cancer is not a malignant tumor that can obtain a longer survival period by aggressive surgical treatment of bone metastasis in the existing literature (22, 23). The current results, in which orthopedic therapeutic surgery showed a positive effect on bone metastasis of liver cancer, may result from a combination of multiple factors, including but not limited to the following: (1) Orthopedic surgery reduced the patient's tumor burden and pain as well as improved the patient's physical condition; (2) In the OTS group, a higher primary tumor resection rate might contribute to a longer survival time in conjunction with orthopedic surgery; (3) We have realized in medical practice that patients who were willing to undergo surgery tend to have good economic conditions and have more opportunities to get better treatment plans.

Considering the limited number of cases, only some of the most representative clinical variables were selected for analysis to meet statistical requirements. In some literature studies, KPS score and surgical treatment of primary lesions are considered to have prognostic significance in HCC patients (6, 9, 11, 24), and these factors were reconfirmed by the current study. Some other variables, such as poor liver function, the presence of ascites, and the presence of metastasis in extra-osseous organs, are also considered risk factors for the survival of patients with bone metastasis of liver cancer (3, 6, 9, 11). We did not include these variables because patients with these characters usually had no indication for surgery.

To note, it is important to follow the indications for surgery when performing surgery on bone metastasis. The patients included in the OTS group were carefully evaluated, and those with surgical contraindications were ruled out. In fact, in our clinical practice, some patients underwent surgery out of a strong desire despite contraindications to surgery (not included in the cohort). Unfortunately, several died due to respiratory failure, liver failure, and other reasons within 1 month post surgery, which went against the original intention of surgical treatment for bone metastasis. Before bone metastasis surgery, surgeons should carefully evaluate the indications and contraindications, clarify the pros and cons for the patient, formulate an individualized treatment plan according to the patient's condition, and fully inform the patient and his family (15, 25).

Although this research provided promising results, it still had the following limitations: (1) The number of patients finally included in the cohort was limited due to the low overall incidence of bone metastasis. To meet the statistical requirement (e.g., sample size/variable size ratio), we only selected limited indicators to evaluate related factors in regression analyses. (2) Also, due to the limited sample size, we did not classify and discuss the details of some treatments (e.g., surgical types for bone lesions). In fact, surgical cure of metastatic disease is generally not achievable attributable to the presence of underlying lesions that cannot be detected by current examination methods and the persistent colonization of bone by circulating tumor cells (25, 26). (3) As a retrospective study, we had some inevitable bias. To reduce

recall bias and nonresponse bias caused by patients failing to follow-up visits, we conducted a follow-up telephone call 3–5 days after the estimated visit date.

In order to further explore the significance of surgery and the prognostic factors for bone metastasis with liver cancer and reduce potential bias, large cohort, multicenter, randomized, and prospective studies are needed.

Conclusion

In conclusion, this study indicates that for patients with bone metastasis of liver cancer who meet certain conditions, orthopedic therapeutic surgery can help improve the quality of life and prolong the survival time. Patients with bone metastasis of liver cancer who have their primary liver lesions resected, undergo orthopedic therapeutic surgery, and have a better physical condition before treatment may have a better prognosis.

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 Ethics Committee of the Third Affiliated Hospital (Eastern Hepatobiliary Surgery Hospital). The patients/participants provided their written informed consent to participate in this study.

Author contributions

QL, CL, FC, and ZW contributed to the original idea and research design. QL, BW, SQ, and ZG contributed to the data collection and data curation. QL, CL, and SJ contributed to the data analysis and image processing. QL, CL, SJ, and MW contributed to the writing—original draft preparation. 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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The priority of liver resection compared with transarterial chemoembolization in hepatocellular carcinoma at BCLC B1 stage: A single-center experience

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Background: This study aimed to compare the efficacy of liver resection (LR) and transarterial chemoembolization (TACE) in the treatment of Barcelona Clinic Liver Cancer B1 (BCLC B1) hepatocellular carcinoma.
Methods: A total of 65 patients with BCLC B1 were divided into the radical (LR group) and TACE groups. Survival analysis was performed using the Kaplan–Meier method. Univariate and multivariate analyses were carried out, and the prognostic factors for survival outcomes were identified using Cox proportional analysis.
Results: The 1-, 3-, and 5-year survival rates and the 1-, 3-, and 5-year progression-free survival (PFS) rates in the LR group ($P = 0.036$) were significantly higher than those in the TACE group ($P = 0.027$). Results of the multivariate analysis demonstrated that tumor distribution (both lobes vs. semi-liver) and treatment strategy (LR vs. TACE) were independent risk factors for the overall survival (OS) [hazard ratios (HRs): 3.926 and 0.479; $P < 0.05$] and PFS (HR: 3.336 and 0.465, $P < 0.05$). LR was associated with increased OS and PFS compared with TACE in patients with BCLC B1 hepatocellular carcinoma.

KEYWORDS
hepatocellular carcinoma, BCLC B1 stage, liver resection, transarterial chemoembolization, safety

Introduction

Liver cancer is the third leading cause of cancer-related deaths worldwide, and the second most lethal cancer in China (1, 2). Hepatocellular carcinoma (HCC) accounts for 75%–85% of primary liver cancer cases (2). With the advancement of treatment and surveillance strategies, the survival rate of patients with HCC has increased in the past few decades, but remains unsatisfactory. Early detection and development of novel treatment strategies are critical to improving the patients' prognosis. The Barcelona Clinic Liver Cancer (BCLC) staging system is commonly used for determining the treatment strategy of patients with HCC. According to this staging

system, radical treatment strategies should be applied to very early and early stage HCC (3). However, most patients are already diagnosed at the intermediate or advanced stages of the disease at the initial visit.

Patients with BCLC B stage HCC presented with large differences in tumor burden, liver function and general conditions. Based on the BCLC recommendations, transarterial chemoembolization (TACE) is the first-line treatment for BCLC B stage HCC. However, not all patients with intermediate-stage HCC benefit from TACE. In addition, the BCLC staging system requires further modification. Bolondi et al. proposed a substage system for BCLC B stage in 2012 (4), which divides intermediate-stage HCC into four substages and provides first-line and alternative treatment strategies for different groups. In recent years, subsequent studies have been performed to validate this system (5–7). According to the Bolondi system, liver resection (LR) is no longer recommended as the primary option. However, its efficacy for patients with intermediate-stage HCC has been validated by several studies (8–11). Thus, the indications of LR for BCLC B stage HCC need further expansion (12–14). Kudo et al. proposed a modified subclassification system similar to the Bolondi criteria (**Table 1**) in 2015 (Kinki criteria) (7). The difference was that they simplified the clinical parameters and provided different treatment strategies for patients with BCLC B1. According to the modified criteria, patients with the B1 stage should undergo radical treatment, such as resection or ablation, and TACE is recommended as a secondary option.

BCLC B1 stage is characterized by compensated cirrhosis and preserved liver function, a Child–Pugh score of 5–7, a tumor burden beyond the Milan criteria, a tumor burden within the up-to-7 criteria (the sum of the largest tumor size and tumor number is not less than 7), and a completely preserved Eastern Cooperative Oncology Group Performance Score (ECOG PS). The Bolondi system recommends TACE as the primary option and liver transplantation or TACE + ablation as an alternative for those with the B1 stage. Ciria et al. performed a retrospective study in 80 patients with BCLC B stage disease (16), and reported the 5-year survival rates were not significantly different between patients who underwent LR and those who underwent TACE. However, the survival rate of patients with B1 stage who underwent LR was significantly better than those with B2, B3, and B4 stages. Thus, the treatment strategy for B1 stage disease remains controversial. The present study aimed to compare the efficacy of LR and TACE in patients with B1 stage. Results were reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology reporting checklist.

TABLE 1 Subclassification of BCLC B stage hepatocellular carcinoma.

Subclassification	Bolondi criteria				Kinki criteria			
	B1	B2	B3	B4	B1	B2	B3a	B3b
Child–Pugh score	5–7	5–6	7	8–9	5–7	5–7	8–9	
Beyond Milan and within up-to-7	In	Out	Out	Any	In	Out	Any In	Any Out
ECOG PS	0	0	0	0–1[a]				
PVT	No	No	No	No				

BCLC, Barcelona clinic liver cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Score; PVT, portal vein thrombosis.
[a]The 2022 updated BCLC strategy patients with PS 1 as advantage (15).

Patients

A total of 65 patients diagnosed with BCLC B1 at the Affiliated Hospital of North Sichuan Medical College between February 2010 and October 2015 were enrolled in the present study. BCLC B1 stage HCC was defined based on the features of patients such as the occurrence of compensated cirrhosis and preserved liver function, a Child–Pugh score of 5–7, occurrence of tumors within the up-to-7 criteria, and a completely preserved ECOG PS. According to different therapeutic strategies, the retrospectively recruited patients were classified into two groups: the radical LR group and the TACE group. The treatment strategies for patients were selected based on the decisions of multidisciplinary teams. The indications for LR included resectable tumors, appropriate residual liver volume, Child–Pugh score of 5–7 without ascites and hypersplenism. The criteria for TACE included a Child–Pugh score of 5–7 and the absence of massive ascites. Moreover, patients who refused to undergo LR were treated with TACE. In order to make a definite clinical diagnosis, all patients underwent radiological examinations such as computed tomography (CT) or magnetic resonance imaging (MRI), and biopsy was performed when the diagnosis was not certain. Patients with (i) a diagnosis of BCLC B1 stage HCC; (ii) good liver function (Child–Pugh score of 5–7); and (iii) good performance status (PS 0) were included in the study. Meanwhile, patients (i) aged <18 years or ≥75 years old; (ii) who received any previous systemic therapy (chemotherapy or target therapy); (iii) previously or currently diagnosed with other malignant tumors; (iv) with active cardiopulmonary disease or infection, except for hepatitis B virus (HBV); and (v) with incomplete data or who were lost to follow-up were excluded. This study was approved by the Ethics Committee of Affiliated Hospital of North Sichuan Medical College, and written informed consent was obtained from all patients prior to the beginning of the study. A flow chart showing the patient selection process is shown in **Figure 1**.

Surgical procedures

The surgical procedures involved both laparoscopic and open radical LR, including nonanatomic regional resection,

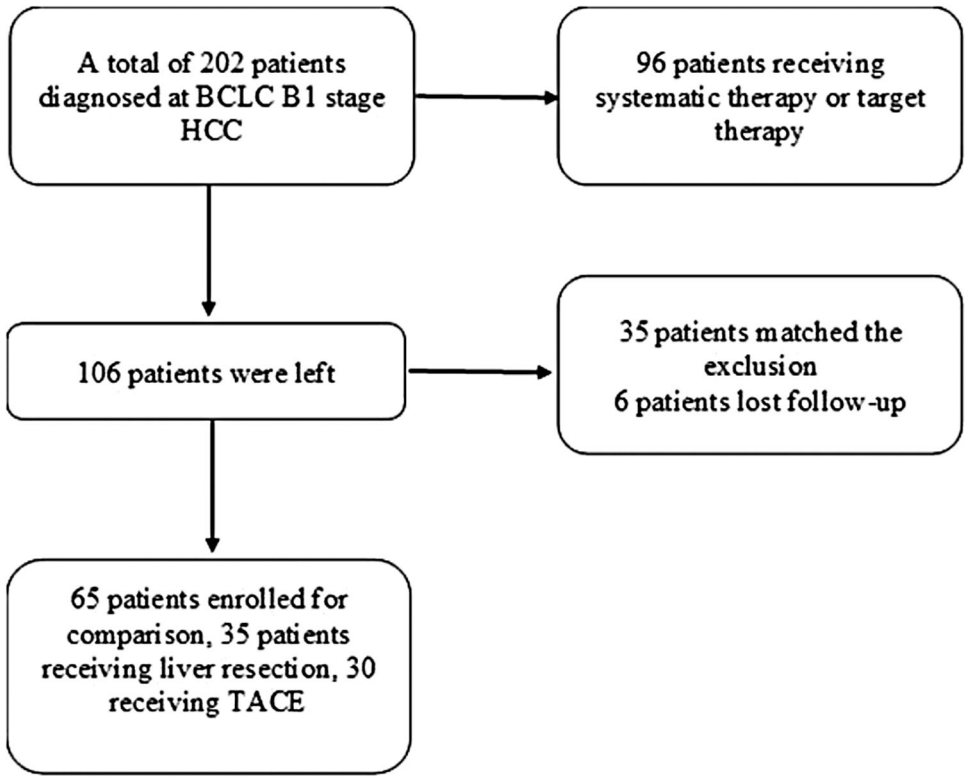

FIGURE 1
Flow chart of patient selection.

segment resection, and lobe resection. The resection line and tumor lesions were identified using intraoperative ultrasound, and patients with positive resection margins were excluded from the present study. Hemihepatectomy was performed as a routine anatomic regional resection with selective hepatic arteries and portal venous amputation. Irregular hepatectomy especially in the right hemi-liver and middle lobe was performed as nonanatomic regional resection, and the Pringle maneuver was performed for 15–20 min with a 5 min clamp-free interval to block the blood flow to the liver. LR was performed using a Cavitron Ultrasonic Surgical Aspirator or harmonic scalpel, while coagulation was performed using a bipolar coagulator. All resected specimens were submitted for histological examination.

All procedures were performed with curative intent, with the aim of R0 resection. The tumor characteristics were determined, and a positive margin was defined as a tumor-free margin of <1 mm. All surgical procedures were performed by surgeons with extensive experience, and the resection line and tumor lesions were identified *via* intraoperative ultrasound. However, positive margins are an inherent problem in LR. Preoperative assessment and precision operation are sufficient to achieve negative resection margins. If a positive resection margin occurs, the procedures performed on the patients are not meaningful, and the long-term survival benefit for patients with resectable HCC is not possible. Since the application of three-dimensional CT reconstruction and intraoperative ultrasound, the relationship between tumor lesions and intrahepatic ducts can be recognized, and seldom positive resection margins have occurred in our medical center in recent years.

Considering that this study aimed to compare the survival benefit of radical LR with that of TACE for BCLC B1 HCC, solitary cases with positive resection margins were excluded.

TACE

Preoperative assessment was performed prior to TACE to determine the liver function, renal function, blood cell count, and PS. A 5-fluorouracil infusion catheter was selectively inserted into the tumor-feeding hepatic arteries. An emulsion of epirubicin (20–40 mg; Pharmorubicin; Pfizer) and Lipiodol (2–10 ml; Guerbet) was injected into the nutrient artery and small gelatin sponge particles were used for embolization. A CT scan was performed 4 weeks after TACE to determine the effect based on the status of iodine oil deposition.

Follow-up

All patients were contacted *via* telephone and e-mail, and the first follow-up was conducted 4 weeks after the operation. If recurrence was not detected, follow-up was performed at an interval of 2 months in the first year. If early recurrence (recurrence within 2 years after surgery) did not occur, follow-up was performed every 6 months. CT or MRI was performed to detect any recurrence or metastasis. The serum alpha-fetoprotein (AFP) level, prothrombin time, and liver function were assessed, and the HBV deoxyribonucleic acid loading was measured if an underlying HBV infection was present.

Overall survival (OS) was defined as the period from the date of treatment to the time of death or last follow-up visit, whereas progression-free survival (PFS) was defined as the period from the date of treatment to the time of disease progression. The Clavien–Dindo grading system of complications was used to assess the postoperative complications after LR or TACE for HCC patients. Follow-up was censored in December 2020.

Statistical analysis

Categorical variables were compared using χ^2 or Fisher's exact tests. Survival analysis was performed using the Kaplan–Meier method and the log-rank test. Univariate and multivariate Cox regression analyses were performed to identify the factors affecting the survival outcomes. Only variables with significance ($P < 0.05$) in the univariable model were included in the multivariable analysis. For all statistical analyses, a P value of <0.05 was considered significant. Statistical analysis was performed using the SPSS 21 software (IBM Corp.) and R-studio (version 4.2.1).

Patient characteristics

Patient characteristics are presented in Table 2. Sixty-five patients diagnosed with BCLC B1 stage HCC between February 2010 and October 2015 were included in the present study. Among them, 57 patients were men and 8 were women, 25 were aged >60 years, 57 had HBV infection, 45 had liver cirrhosis, 18 had more than three tumors, and 8 had more than four tumors. Patients with HCC and HBV infection were treated with entecavir (0.5 mg) daily throughout their lifetime. Five patients presented with tumor lesions in both lobes, two of whom underwent right semi-hepatectomy plus regional left liver lobe resection (one tumor lesion located in the inferior left lateral lobe). The other three patients underwent anatomic segment resection plus radiofrequency ablation. Of them, two patients presented with tumor lesions distal to the liver capsule, and one patient presented with a tumor lesion proximal to the large hepatic vein. No perioperative surgery-related deaths were observed, and bile leakage, pulmonary infection, or liver failure occurred in several patients. The demographic characteristics of these two groups were comparable. Among all patients, only two developed severe postoperative complications (grade 3/4). In

TABLE 2 Comparison of baseline characteristics of enrolled patients.

Clinicopathological factors	LR group ($n = 35$)	TACE group ($n = 30$)	P value
Gender			
Male	30	27	0.716
Female	5	3	
Age			
60	12	13	0.455
≤60	23	17	
HBsAg			
Positive	30	27	0.716
Negative	5	3	
AFP (ng/ml)			
>400	22	8	**0.004**
≤400	13	22	
Child–Pugh score			
7	6	4	0.937
5–6	29	26	
Liver cirrhosis			
Yes	24	21	0.901
No	11	9	
Tumor number			
≥3	10	8	0.864
=2	25	22	
Tumor number			
>3	4	4	1.000
≤3	31	26	
Largest tumor size			
>4 cm	15	12	0.816
≤4 cm	20	18	
Largest tumor size			
>3 cm	30	25	1.000
≤3 cm	5	5	
Tumor distribution			
Both lobes	5	3	0.716
Semi-liver	30	27	
Tumor capsule			
Complete	24	16	0.084
Infiltration	11	14	

HBsAg, hepatitis B surface antigen; AFP, α- fetoprotein; LR, liver resection; TACE, transarterial chemoembolization.

the TACE group, fever, nausea, and abdominal pain (which were postembolization syndrome features) were the most common complications. According to the Clavien–Dindo grading system, no significant differences in any of the complications according to grade (Table 3).

OS analysis

The median follow-up time was 63 months, while the median OS time of all patients was 50 months. The median OS time in LR group was not reached, while that in TACE group, was 37 months [95% confidence interval (CI): 30.31–43.70 months; hazard ratio (HR): 0.482; 95% CI: 0.245–0.951; $P = 0.027$]. The 1-, 3-, and 5-year OS rates were 98.5%, 67.7%, and 46.2%, respectively. The 1-, 3-, and 5-year OS rates in LR group were 97.1%, 80.0%, and 57.1%, respectively. The 1-, 3-, and 5-year OS rates in TACE group were 100.0%, 53.3%, and 33.3%, respectively. Notably, patients in the LR group had better survival outcomes compared with those in the TACE group ($P = 0.027$) (Figure 2A).

Subgroup analysis was performed according to the baseline characteristics. The median OS time in the LR group was significantly longer than that in the TACE group in patients aged >60 years, with a serum AFP level of >400 (ng/ml), with a Child–Pugh score of 5–6, with 2–3 tumor lesions, whose largest tumor size was >3 cm, and whose tumor lesions were located within the semi-liver ($P < 0.05$) (Figure 3A).

TABLE 3 Postoperative complications in the two patient group *n* (%).

	Total ($n = 65$)	LR group ($n = 35$)	TACE group ($n = 30$)	*P* value
Complications	13 (20.0)	8 (22.9)	5 (16.6)	0.534
Grade 1	6 (9.2)	4 (11.4)	2 (6.7)	
Grade 2	5 (7.7)	3 (8.6)	2 (6.7)	
Grade 3	1 (1.5)	0 (0)	1 (3.3)	
Grade 4	1 (1.5)	1 (2.9)	0 (0)	
Grade 5	0 (0)	0 (0)	0 (0)	0.856
Minor complications (1–2)	11 (16.9)	7 (20.0)	4 (13.3)	0.475
Major complications (3–4)	2 (3.1)	1 (2.9)	1 (3.3)	1.000

LR, liver resection; TACE, transarterial chemoembolization.

PFS analysis

The median PFS time of all patients was 30 months (95% CI: 19.85–40.15 months); the median PFS time in the LR and TACE groups was not reached, while that in the TACE groups was 21 months (95% CI: 8.92–33.08 months; HR: 0.529; 95% CI: 0.281–0.993; $P = 0.036$). The 1-, 3-, and 5-year PFS rates were 89.2%, 44.6% and 36.9%, respectively. The 1-, 3-, and 5-year PFS rates in LR group were 97.1%, 57.1% and 45.7%, respectively. The 1-, 3-, and 5-year PFS rates in TACE group were 80.0%, 30.0%, and 26.7%, respectively. Notably, patients in the LR group exhibited significantly lower recurrence rates than those in the TACE group ($P = 0.036$) (Figure 2B).

Subgroup analysis was performed based on the clinicopathological characteristics, and the PFS rate in the LR

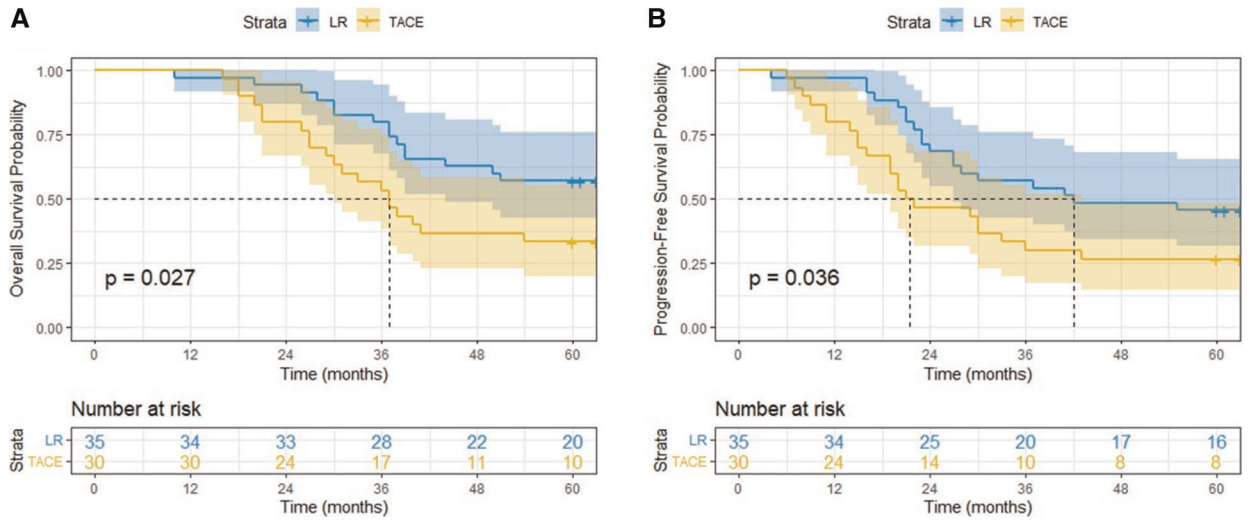

FIGURE 2
Overall survival (A) and progression-free survival (B) curves of patients with BCLC-B1 stage HCC treated by liver resection or transarterial chemoembolization.

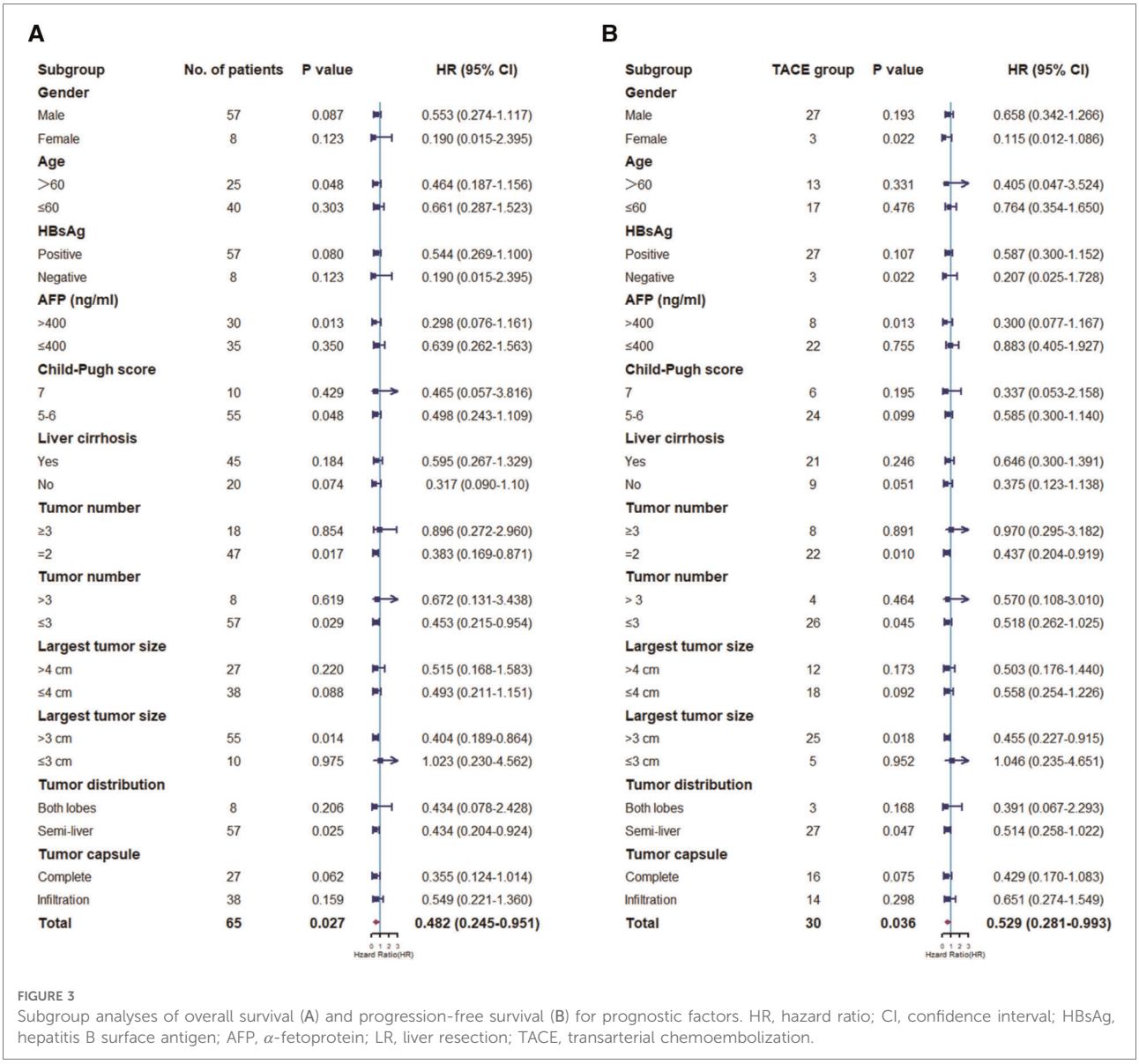

FIGURE 3
Subgroup analyses of overall survival (A) and progression-free survival (B) for prognostic factors. HR, hazard ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen; AFP, α-fetoprotein; LR, liver resection; TACE, transarterial chemoembolization.

group was significantly lower than that in the TACE group in female patients, patients with negative results on HBsAg test, patients with a serum AFP level of >400 (ng/ml), patients with 2–3 tumor lesions, patients whose largest tumor size was >3 cm, and patients whose tumor lesions were located within the semi-liver ($P < 0.05$) (Figure 3B).

Univariate and multivariate analyses of risk factors for OS and PFS

A total of 12 parameters were assessed in the univariate analysis, and tumor distribution and treatment strategy were independent risk factors for OS and PFS ($P < 0.05$). The multivariate analysis demonstrated that tumor distribution (both lobes vs. semi-liver) (HR: 3.926, 95% CI: 1.659–9.292, $P = 0.002$) and treatment strategy (LR vs. TACE) (HR: 0.410, 95% CI: 0.206–0.820, $P = 0.012$) were independent risk factors for OS. Similarly, the multivariable Cox proportional hazards model for PFS identified the tumor distribution (both lobes vs. semi-liver) (HR: 3.336, 95% CI: 1.429–7.788, $P = 0.005$) and treatment strategy (LR vs. TACE) (HR: 0.465, 95% CI: 0.247–0.876, $P = 0.018$) as independent risk factors (Table 4).

Discussion

According to the BCLC guidelines, intermediate-stage HCC is characterized by varied tumor burden and liver function, and TACE is recommended as the first-line treatment for this

TABLE 4 Univariate and multivariate analysis of OS and PFS.

Variable	OS				PFS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Gender								
Male	1.641 (0.502-5.342)	0.412			1.269 (0.452-3.564)	0.651		
Female								
Age								
>60	0.632 (0.309-1.291)	0.208			0.627 (0.324-1.212)	0.165		
≤60								
HBsAg								
Positive	1.751 (0.536-5.722)	0.354			0.775 (0.326-1.844)	0.564		
Negative								
AFP (ng/ml)								
>400	0.856 (0.438-1.674)	0.650			0.595 (0.315-1.125)	0.110		
≤400								
Liver cirrhosis								
Yes	1.033 (0.496-2.152)	0.932			0.820 (0.430-1.564)	0.547		
No								
Tumor number								
≥3	1.131 (0.554-2.312)	0.735			0.954 (0.478-1.905)	0.895		
=2								
Tumor number								
>3	1.743 (0.722-4.206)	0.216			1.608 (0.674-3.840)	0.285		
≤3								
Largest tumor size								
>4 cm	0.757 (0.381-1.504)	0.427			0.721 (0.381-1.362)	0.313		
≤4 cm								
Largest tumor size								
>3 cm	0.674 (0.294-1.546)	0.352			0.697 (0.308-1.577)	0.387		
≤3 cm								
Tumor distribution								
Both lobes	3.135 (1.362-7.214)	0.007	3.926 (1.659-9.292)	0.002	2.692 (1.185-6.115)	0.018	3.336 (1.429-7.788)	0.005
Semi-liver								
Tumor capsule								
Complete	0.989 (0.503-1.946)	0.975			1.239 (0.668-2.297)	0.497		
Infiltration								
Treatment Group								
LR	0.480 (0.245-0.939)	0.032	0.410 (0.206-0.820)	0.012	0.534 (0.288-0.988)	0.046	0.465 (b>0.247-0.876)	0.018
TACE								

OS, over survival; PFS, progression-free survival; HR, hazard ratio; CI; confidence interval; HBsAg, hepatitis B surface antigen; AFP, α- fetoprotein; LR, liver resection; TACE, transarterial chemoembolization.

condition. However, recent studies have reported the benefits of radical treatment in patients with BCLC B stage HCC. In addition, several researchers have proposed expanding the indications for LR in the treatment of intermediate-stage HCC. Bolondi et al. introduced a substaging system for BCLC B stage in 2012 (4), which classified BCLC B into four stages. This staging system was validated in subsequent studies. Kudo et al. developed this system and proposed a new substaging system (Kinki criteria) (7). Despite the similarities with Bolondi's system, the Kinki criteria are simpler and easier to apply, and resection and ablation are included as treatment options for patients with substage B1 disease. Although BCLC

B stage HCC patients had a PS of 0–1 based on previous BCLC strategy, the Bolondi's criteria stressed that the ECOG PS score for the BCLC B1 substage was 0. Therefore, only BCLC B1 stage patients with PS 0 were included and fulfilled the 2022 updated staging criteria (15). Both systems define patients with tumors within up-to-7 criteria and with good liver function as having a BCLC B1 substage; however, the treatment recommendations differ. Therefore, the present study compared the survival benefits of LR and TACE in patients with the BCLC B1 stage.

The results of the present study demonstrated that LR significantly prolonged the OS and PFS of patients with BCLC B1 stage compared with those in the TACE group. Wang et al. and Scaffaro et al. performed two studies to validate Bolondi's criteria (17, 18). These findings demonstrated that patients with BCLC B1 stage who underwent TACE and LR had median OS times of 2.4 and 2.8 years, respectively. Arizumi et al. performed a retrospective study in 2015 to validate the Kinki criteria (6). All patients who underwent TACE and were diagnosed with BCLC B1 subclass had a median OS time of 3.0 years. This group performed another study in 2016 to validate the Kinki criteria (19). A total of 156 patients with BCLC B1 stage were enrolled in the study, of whom 25 underwent LR and 16 underwent radiofrequency ablation; the results demonstrated that the median OS time of patients with BCLC B1 stage was 4.3 years, which was similar to the results of the present study.

Taken together, radical treatment may provide better survival outcomes compared with TACE in patients with BCLC B1 subclass. However, whether LR should be recommended as a first-line treatment for patients with BCLC B stage remains controversial. Wada et al. discussed the selection criteria for LR in patients at BCLC B stage (20). They divided the patients into three groups according to the tumor burden; results showed that patients with up to three lesions (<5 cm) had a significantly improved survival rate compared with other patients treated with LR; moreover, the 3- and 5-year survival rates were 87.4% and 75.2%, respectively, which were comparable with the survival rates reported in the present study. However, the recurrence outcomes in our study were notably improved compared with those reported by Wada et al.; the 3- and 5-year PFS rates in our study were 54.3% and 45.7%, respectively, while those in Wada et al.'s study were 34.4% and 18.8%, respectively. Considering the differences in long-term outcomes, patients in the present study had a lower microscopic intrahepatic metastasis and a lower average serum AFP level. As demonstrated by numerous studies, microvascular invasion and high preoperative tumor marker levels were reported to be independent risk factors for postoperative recurrence (21, 22).

Recently, Chen et al. used the Markov model to compare the efficacies of LR and TACE for BCLC stage B1. They simulated a randomized controlled trial (RCT) with a follow-up period of 15 years. The median OS was 43.3 months, with the 3- and 5-year survival rates of 41.3% and 30.6%, respectively. Patients were recruited between 2008 and 2014. Subsequent advancements in surgical concepts and equipment have validated the benefits of LR compared with TACE for BCLC stage B. Taken together, LR is a potentially curative therapy, whereas TACE is a palliative therapy that leaves viable tumor cells in the liver tissue. Thus, whether the indication for LR in selective patients with BCLC B stage should be expanded remains controversial. Hence, high-quality RCT and systematic reviews should be performed to resolve this controversy. A recent systematic review supported the role of LR as a treatment option for BCLC B HCC, and emphasized the need to refine the criteria for LR (23).

The present study focused on a subclass of BCLC B HCC, BCLC B1, which includes patients with favorable liver function and low tumor burden. According to the definition of BCLC B1, the tumor burden was beyond the Milan criteria but within the up-to-7 criteria. Among all the patients who underwent LR, 25 (71.4%) presented with no more than two tumors and were good candidates for LR, either lobe resection or segment resection. A total of five patients had tumor lesions located in both lobes, two of whom underwent right semi-hepatectomy plus regional left liver lobe resection (one tumor lesion located in the inferior left lateral lobe). The other three patients underwent anatomic segment resection plus radiofrequency ablation. In addition, two patients presented with tumor lesions located at the long distal to the liver capsule, while one patient presented with tumor lesions proximal to the large hepatic vein; all three patients were classified as having unresectable HCC. Therefore, these patients did not undergo liver transplants. It is well known that the incidence of HCC and disease-related mortality remains high in China; approximately 50% of new-onset HCC cases worldwide are diagnosed in China every year. A large number of patients are on the waiting list to receive a liver transplant. As the indications for liver transplantation in HCC patients remain limited, the majority of medical centers in China still recommend the Milan Criteria as the golden standard for selecting HCC patients who require a liver transplant. In our clinical practice, patients diagnosed with BCLC B1 stage HCC have not yet been identified as candidates for liver transplantation. With regard to the safety of LR, no perioperative surgery-related deaths were observed among the enrolled patients; meanwhile, several patients experienced bile leakage, pulmonary infection, and liver failure, and only two patients developed severe postoperative complications (grade 3/4).

Both surgery and TACE require good liver function based on the Child–Pugh score or albumin–bilirubin grade, due to the risk of liver function deterioration after treatment. The percentage of patients with a Child–Pugh score of 7 (Child

class B) was comparable between the LR and TACE groups. According to current guidelines, only patients with a Child class A liver function are candidates for LR and TACE. However, previous studies have demonstrated the safety and efficacy of LR and TACE therapy in patients with HCC and Child class B HCC (24, 25). Although Child class B classification is a negative risk factor for the survival of patients treated with LR and TACE, the negative risk factor should not be considered an absolute contraindication and should be challenged with the balance between the potential benefit and the possibility of liver function deterioration (26). In the present study, 10 patients with a Child–Pugh score of 7 underwent LR and TACE, and no postoperative mortality was reported. Among them, two patients had severe postoperative complications (grade 3–4). The available data probably revealed the safety and efficacy of LR and TACE for selected patients (Child score of 7) with Child class B. As regarding the impact of an underlying liver disease on HCC recurrence after treatment, the etiology of HCC differs between different regions worldwide. In China, approximately 90% of all HCC cases are derived from chronic HBV infection—liver cirrhosis —HCC, also known as trilogy. However, alcohol consumption and hepatitis C virus (HCV) infection are the primary causes of HCC in Europe and North America. The treatment of underlying liver disease has important impact on HCC recurrence and prognosis after radical or regional therapies (27–30). In our clinical practice, patients with HBV infection receive oral entecavir treatment daily throughout their lifetime; if tolerance occurred, tenofovir fumarate was used as antiviral therapy. Alcohol abuse has been recognized to play a potential role in the incidence and recurrence of HCC, and previous studies have revealed its prognostic impact in patients with HBV-related liver disease (31). According to the World Health Organization, alcohol abuse is defined as daily alcohol intakes of >25 mg in men and >15 mg in women. To decrease the incidence and recurrence of HCC, we recommend alcohol abstinence in all patients once diagnosed.

This study had several limitations. First, this was a nonrandomized controlled study conducted at a single center; therefore, a selection bias may exist. Second, the sample size of this study was small and not representative of all patients with HCC. Therefore, large-scale, multicenter, randomized controlled studies are required.

In conclusion, LR significantly prolonged the OS time and reduced the recurrence rate (with the risk reduced by 59%) of patients with BCLC B1 stage compared with TACE. In addition, tumor lesions distributed in both lobes of the liver and treatment strategy (LR vs. TACE) were independent risk factors for OS and PFS. Tumor lesions distributed in both lobes of the liver increase the risk of mortality (by four fold) and postoperative recurrence (by threefold).

The results of the present study favor the Kinki criteria over the Bolondi's criteria, suggesting that LR can benefit patients with BCLC B1 stage compared with TACE. Taken together, the results of the present study indicate that LR is associated with increased OS and PFS compared with TACE in patients with BCLC B1 HCC.

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 the Ethics Commitment of Affiliated Hospital of North Sichuan Medical College. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conception and design: P-SY and J-SL. Administrative support: PS-Y. Provision of study materials or patients: JN-L and YL. Collection and assembly of data: YL and BW. Data analysis and interpretation: PS-Y and J-NL. Manuscript writing and final approval: All authors. 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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Volume and flow modulation strategies to mitigate post-hepatectomy liver failure

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Introduction: Post hepatectomy liver failure is the most common cause of death following major hepatic resections with a perioperative mortality rate between 40% to 60%. Various strategies have been devised to increase the volume and function of future liver remnant (FLR). This study aims to review the strategies used for volume and flow modulation to reduce the incidence of post hepatectomy liver failure.

Method: An electronic search was performed of the MEDLINE, EMBASE and PubMed databases from 2000 to 2022 using the following search strategy "Post hepatectomy liver failure", "flow modulation", "small for size flow syndrome", "portal vein embolization", "dual vein embolization", "ALPPS" and "staged hepatectomy" to identify all articles published relating to this topic.

Results: Volume and flow modulation strategies have evolved over time to maximize the volume and function of FLR to mitigate the risk of PHLF. Portal vein with or without hepatic vein embolization/ligation, ALPPS, and staged hepatectomy have resulted in significant hypertrophy and kinetic growth of FLR. Similarly, techniques including portal flow diversion, splenic artery ligation, splenectomy and pharmacological agents like somatostatin and terlipressin are employed to reduce the risk of small for size flow syndrome SFSF syndrome by decreasing portal venous flow and increasing hepatic artery flow at the same time.

Conclusion: The current review outlines the various strategies of volume and flow modulation that can be used in isolation or combination in the management of patients at risk of PHLF.

KEYWORDS

post hepatectomy liver failure, future liver remnant, flow modulation, liver resection, risk mitigation, volume modulation

Introduction

Post hepatectomy liver failure (PHLF) is the most common cause of death following major hepatic resections (1) but despite recent innovations to improve outcomes following hepatic resection the incidence of PHLF has still been reported as between 1% to 35%, with a perioperative mortality rate as high as 40% to 60% in the last decade (2, 3). The most commonly used definitions include '50-50' criteria which was predictive of 60-day mortality in a series of 775 hepatic resections and the International Study Group of Liver Surgery (ISGLS) consensus definition for PHLF. This describes three grades of PHLF with a mortality ranging from 0% for grade A to 54% for grade C (4).

Identification of patients 'at risk' is essential with risk factors including advanced age, diabetes mellitus, increased BMI, preoperative chemotherapy and underlying liver disease such as fibrosis and cirrhosis (5). However, one of the most important risk factors is an inadequate future liver remnant (FLR) volume which has been defined as FLR volume/Total Liver volume (TLV) of <25% in those with a healthy background liver and in those with background liver disease, FLR/TLV of >40% is required (6, 7). Given the significant morbidity and mortality associated with PHLF numerous strategies have been used to try and mitigate the risk of it developing. The aim is to increase the volume and function of future liver remnant and ensuring that the portal venous flow and pressures are appropriate to prevent the small for size flow syndrome.

This study aims to review the current literature available relating to flow and volume modulation of the FLR to mitigate PHLF.

Methods

An electronic search was performed of the MEDLINE, EMBASE and PubMed databases from inception of the database to January 2022. Prospective and retrospective clinical studies that investigated strategies to increase the FLR or modulate blood flow to the liver prior to liver resection were included. Conference abstracts, letters and editorials were excluded. The following search strategy comprising MeSH headings and truncated word searches to identify all articles published relating to volume or flow modulation prior to liver resection was used: future liver remnant, post hepatectomy liver failure, portal vein embolization, embolization of the portal venous branches, hepatic vein embolization, dual vein embolization, bi-embolization, liver venous deprivation, Associating liver partition and portal vein ligation for staged hepatectomy, ALPPS, portal vein ligation. The references of included studies were also reviewed to identify additional studies.

Volume Modulation

Portal vein embolization/ligation

Portal vein embolization is a well-established technique for preoperative augmentation of the FLR and has been used for approximately 30 years (8). Several different approaches have been described with either an ipsilateral or contralateral approach being most common. The main advantage of the former being the avoidance of directly puncturing the FLR and the potential complications associated with this whereas the contralateral approach is technically easier allowing straight catheterization of the right portal vein (9). However, if segment 4 requires embolization this can be challenging from a contralateral approach. Embolization of segment 4 in addition to the right portal vein has shown increased hypertrophy and increased kinetic growth rate when compared to right PVE alone (10, 11). As an alternative for the access to portal vein, trans-ileocecal approach is used occasionally. It is useful for cases where direct puncture of intrahepatic portal branches is difficult, for example, huge liver tumors (12). The combination of trans-ileocolic portal embolization with associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) has also been reported, which does not require dissection of the hilum in the first stage and may be good in the context of major hepatectomy for hilar cholangiocarcinoma (13).

PVE is generally considered to be a safe procedure with low rates of morbidity and mortality with the most common complication being a 'post-embolization syndrome' characterized by fever, abdominal pain and elevation of liver transaminases (14). More serious complications are fortunately rarer and include portal vein thrombosis, hematoma and abscess formation with an incidence of each being <1%. In a large systematic review non-target embolization occurred in 0.6%. In the same study complications led to un-resectability in only 0.4% of patients with an overall procedure mortality rate of 0.1% (15, 16).

Portal vein embolization is associated with high rates of technical success with rates >95% consistently reported. Hypertrophy of the FLR is reported as a mean of 38 – 49% in systematic review and meta-analysis with hypertrophy of over 50% in the context of additional segment 4 embolization. In the context of fibrosis or cirrhosis a rate of hypertrophy more than 10% can generally be considered safe to proceed with resection whereas in a normal liver this is more than 5% (17, 18). The majority of FLR hypertrophy occurs within the first 3-4 weeks with the maximum volume usually achieved by about 6 weeks.

Whilst FLR hypertrophy with PVE is effective perhaps the most frequent limitation to its use is that of disease progression whilst awaiting adequate hypertrophy. It has been hypothesized that tumor progression may be accelerated by the release of

growth factors released as a consequence of PVE (19). However, longer term follow-up of patients undergoing liver resection with versus without PVE is conflicting with some studies demonstrating no difference in hepatic recurrence or overall survival up to 5 years (20). Whilst other show inferior survival (21, 22). Whilst there is variation in the reported rates of successful resection following PVE commonly approximately 70-75% of patients ultimately complete the treatment sequence (21). In a systematic review and meta-analysis of 44 studies including 1791 patients the overall morbidity rate was 21.7% with a mortality of 3.3%. Primary liver failure (0.4%) or liver failure in combination with multiorgan failure (1.2%) was the cause of death in over 50% of cases (15).

Portal vein ligation (PVL) is an alternative to PVE and most frequently used in the context of two stage hepatectomy (TSH) whereby the FLR is cleared of tumor along with ligation of the right portal vein to induce hypertrophy in the FLR. PVE and PVL have been compared in meta-analysis with a comparable morbidity and mortality profile along with similar percentage increase in FLR. There was also no difference between the groups with regards to disease progression precluding liver resection (23).

Associating liver partition with portal vein ligation for staged hepatectomy

To try and mitigate the progression of disease whilst waiting for adequate hypertrophy various strategies have been developed to promote a more rapid hypertrophy thus allowing resection to take place at an earlier stage. The initial 'classic' ALPPS demonstrated FLR hypertrophy rates of 75% allowing the second stage of resection to take place after a median of 9 days (24). Although this new approach showed very rapid hypertrophy this was offset by a significant morbidity and mortality with data from the International ALPPS Registry showing a 90-day mortality of 12% and major complication rate (Clavien-Dindo ≥3b) of 27% (25). Outcomes for elderly patients and those undergoing resection for hepatocellular carcinoma, peri-hilar cholangiocarcinoma and intrahepatic cholangiocarcinoma were even worse leading to the adoption of ALPPS for primarily colorectal liver metastases (26). Due to the significant morbidity associated with ALPPS various modifications were proposed to the original technique to try and improve outcomes. These include partial ALPPS (partial transection with PVL), hybrid ALPPS (complete transection with PVE between 2 stages), RALPPS (radiofrequency ablation of transection line with PVL), mini ALPPS (partial transection with PVE *via* inferior mesenteric vein) and laparoscopic ALPPS (27, 28). In addition to modifications of the technique, timing of the second stage is also important with a slight delay favored by some units. With the second stage performed after about 2 weeks (29). The recent 'benchmarking' of ALPPS using the registry of 1036 patients identified completion of stage 2 >96%, PHLF after stage 2 <5%, overall morbidity for stage 1 and 2 of <65% and major complications <38% and the 90-day mortality of <5% indicating similar outcomes to other types of major hepatectomy (30).

Despite the high morbidity and mortality associated with ALPPS there is evidence from the Scandinavian LIGRO Trial of increased resectability rates when compared with those undergoing PVE although the 90-day mortality remained high particularly in the context of the known high recurrence rate (31). 'Salvage' ALPPS has also developed in the setting of inadequate hypertrophy following PVE with mean FLR hypertrophy for this approach being between 57-65% (32–34)

Combined portal and hepatic vein embolization

Given the concerns regarding disease progression whilst waiting for adequate hypertrophy with PVE and the high morbidity and mortality associated with ALPPS alternative methods of modulating the FLR have been sought. Initially reported by Hwang et al. in 2009, embolization of the portal vein and then hepatic venous outflow sequentially after several weeks has been shown to be safe and effective. Initial reports show an increase in FLR from 35% pre-PVE to 40% 1-2 weeks after PVE and finally 44% 2 weeks after hepatic vein embolization (HVE) (35). Given the promising initial reports the technique has been further modified to perform embolization of the portal and hepatic veins simultaneously. This has been given multiple different names including liver venous deprivation (LVD), bi-embolization, dual vein embolization (DVE) and Radiological Simultaneous Porto-hepatic Vein Embolization (RASPE) (36–38). Although retrospective in nature the available studies demonstrate that DVE is a safe, low morbidity procedure with the most frequently cited complication being a 'post-embolization' syndrome characterized by fever and abdominal pain with treatment being supportive. Studies comparing the hypertrophy of the FLR between PVE and DVE show a superior percentage hypertrophy with DVE, 59% versus 48% (p=0.020) and 61% versus 29% (p=<0.001) in two of the larger studies (38, 39). Similarly the kinetic growth rate associated with DVE also appears to be superior to PVE alone with one study showing a rate of 3.5 versus 2.5 (sFLR/week) (p=<0.001) with kinetic growth rate being an important predictor of postoperative morbidity and mortality after liver resection in those with a small FLR (40). A recent meta-analysis showed that significantly more patients progress to liver resection following DVE 11% versus 24% (p=0.009). In that study only 3/20 patients didn't progress to surgery due to inadequate FLR whereas 23/79 following PVE alone still couldn't undergo surgery due to inadequate FLR. The most common other reason for not undergoing surgery was disease progression. Following liver resection rates of major complications appeared lower as did the incidence of PHLF with DVE, 13% versus 22% (p=0.13) although this did not reach statistical significance. Post-

operative mortality was also improved following DVE (41). Whilst several randomized studies are currently in progress comparing PVE to DVE (DRAGON 1 –Training, Accreditation, Implementation and Safety Evaluation of Combined PVE/HVE – ClinicalTrials.gov NCT04272931 and HYPER-LIV01 the outcomes from retrospective studies, and meta-analysis of these, suggests that DVE is associated with improved hypertrophy and perhaps lower complications, particularly PHLF than PVE alone (42).

Only one retrospective study has directly compared outcomes following DVE to ALPPS. That study involved 209 patients of whom 124 had DVE and 85 underwent ALPPS. This showed that hypertrophy was greater with ALPPS with higher rates of surgical resection (72% versus 91%, p=<0.001). Although operative duration, blood loss and length of stay were better with LVD there was no difference in major complications or mortality (43). While the studies have demonstrated a greater increase in FLR volume with LVD, PHLF was encountered in 13% of the patients and it must be remembered that volume doesn't necessarily equate to function. Dynamic 99mTc-mebrofenin hepatobiliary scintigraphy with single photon emission computed tomography is one method that has been used to quantitively assess liver, and FLR, function (44). The FLR will be assessed not only for change in volume but also function using 99mTc-mebrofenin SPECT-CT and will add considerably to the evidence base for PVE/DVE (43). Guiu et al. investigated the impact of PVE and LVD using 99mTc-mebrofenin SPECT-CT measuring function and volume at day 7, 14 and 21 post procedure. FLR function and volume was significantly greater at all time points with LVD as opposed to PVE (45).

Trans-arterial chemoembolization combined with portal vein embolization

Hypertrophy of the FLR is much more variable in patients with chronic liver disease undergoing liver resection increasing the risk of PHLF. This is also the case following PVE in this patient group. The addition of TACE prior to PVE for patients with HCC has been demonstrated to increase FLR hypertrophy compared to PVE alone (46). The additional benefit of this approach is the arterial embolization provides treatment to the tumor in the embolized lobe reducing the risk of disease progression. FLR hypertrophy using this sequential technique ranged between 7 – 56% with typically 2 – 3 weeks interval between the two procedures (47). The main concern with this approach is that of liver infarction and therefore care must be taken to embolize as distally as possible as well as modifications to the technique used. Some have proposed reversing the sequence of procedures with PVE performed prior to TACE suggesting that the degree of hypertrophy is dependent on the period of time between PVE and hepatectomy and that performing PVE first may reduce the likelihood of liver infarction and abscess formation (47).

It seems likely that there will be a place for all different methods of volume modulation for those with a predicted low FLR prior to major hepatectomy. PVE and two stage hepatectomy with PVL are well established with a good safety profile and will continue to be used routinely by a large number of centers. As experience with newer techniques such as DVE increases and the evidence base grows for this approach it is feasible that this will become the predominant method for FLR volume modulation for colorectal liver metastases as well as primary liver cancers. It might also be that the role of PVL will be limited to the setting of ALPPS. The role for ALPPS is harder to predict with opinion still divided over its role. Whilst acceptable results have now been demonstrated in high volume centers (30) there remains a reluctance by many to adopt this as the initial method for FLR modulation preferring to use it as a 'salvage' procedure after inadequate hypertrophy with PVE/DVE. Traditionally ALPPS has been reserved for patients with CRLM due to the initial very high morbidity and mortality associated with its use in hepatocellular carcinoma and cholangiocarcinoma. More recently the role of ALPPS for HCC and both perihilar and intrahepatic cholangiocarcinoma has been re-explored with outcomes comparable to more traditional approaches most probably related to modification of the technique with partial ALPPS and a minimally invasive approach used to reduce surgical stress (48–50).

Flow modulation

Following major hepatic resections, the rise in portal venous flow in the presence of low remnant volume culminate into small for size flow (SFSF) syndrome (51). The key mechanism is the whole maintained portal flow diverted to remnant liver causing sinusoidal congestion and damage to endothelial lining leading to hemorrhage and architectural disruption and hepatocyte injury. High portal vein pressures (PVP) also result in hepatic artery buffer response by reducing hepatic artery pressures leading to ischemic biliary injury and cholangitis (52) These changes are irreversible and liver parenchyma loses its capability to regenerate. The incidence of SFSF is directly dependent on transhepatic portal vein and hepatic artery flow, portal pressures and volume of remnant liver. Portal venous flow of 250ml/min/100g is considered as the upper limit for SFSF syndrome by Troisi et al. (52). Thus, surgical techniques that decrease portal vein flow/100g and portal vein pressure, as well as increase hepatic artery flow/100g following extended hepatic resections can prevent the occurrence of SFSF (53). Table 1 summarises papers describing flow modulation strategies to mitigate SFSF following liver resection.

Portal flow modulation was initially applied in living donor liver transplantation. Techniques including portal flow diversion, splenic artery ligation and splenectomy are

TABLE 1 Studies reporting portal flow modulation techniques after liver resection to prevent PHLF.

Study	Procedure and indication	Number of patients	Intervention	Condition	Outcome	Outcome parameters
Golriz et al. (52) (Animal model)	Extended liver resection	40 pigs	Portocaval shunt		Improved hepatic artery flow	PVP reduced from 16 ± 1.29 to 9.9 ± 0.66 mmHg and HAP increased from 17.77 ± 2.8 to 24.07 ± 2.08 ml/min/100 g
Arakawa et al. (55) (Animal model)	90 percent hepatectomy	25 rats	Splenectomy		Improved liver regeneration	Hemeoxygenase-1 and its messenger RNA expression increased
Ren et al. (61) (Animal model)	50%, 60%,70% and 90% hepatectomy	160 rats	Splenectomy		Improved liver regeneration and liver functions	Increased DNA synthesis and proliferation cell nuclear antigen.
Hammond et al. (70) (Animal model)	80 percent hepatectomy	24 pigs	Portocaval shunt and terlipressin		Increased hepatic artery flow and reduced the incidence of PHLF.	HAF increased to 73ml/min from 40ml/min.
Jo et al. (71) (Animal model)	90% hepatectomy		Terlipressin		Optimize liver regeneration and improved survival	PVP reduced to 5.8 ± 1.1 from 7.7 ± 2.2 mmHg one hour after hepatectomy
Rhaiem et al. (72)	Major hepatectomy	10 patients	Somatostatin	Cirrhosis	Effective portal flow modulation	3 mm median reduction in PVP
Takamatsu et al. (73)	Right hepatectomy for HCC	1 patient	Splenectomy	Cirrhosis	Reduced the incidence of PHLF	PVP reduced from 32 to 23
Kohler et al. (74)	Major liver resection for HCC, IHCC and CRLM	75 patients	Terlipressin	Cirrhosis, Child Pugh A and B	No difference	
Abbas et al. (75)	Major liver resections Indication not mentioned	42 patients	Terlipressin	Cirrhosis, Child A and B	No difference	
Mahdy et al. (76)	Major liver resections	25 patients	Terlipressin	Not mentioned	Improved intraoperative hemodynamic and blood loss	PVP reduction from 17.88 ± 7.32 to 15.96 ± 6.55
Li et al. (77)	Major liver resections	65 patients	Terlipressin	Cirrhosis	Reduced the incidence of PHLF and ascites.	Ascites volume decreased from 730ml to 350ml and PVP reduced from 15.8 ± 2.6 to 14.3 ± 2.9
Pei et al. (78)	Major and minor liver resections	184 patients	Splenectomy	Cirrhosis, Child A and B	Significantly improved liver functions	Improved liver functions in Child B patients
Carrapita et al. (79) (Animal model)	85% hepatectomy	48 rats	Splenic artery ligation		Increased hepatocellular viability and regeneration	Increased viability of cells and decreased oxidative stress.

employed to reduce the risk of SFSF syndrome by decreasing portal venous flow and increasing hepatic artery flow at the same time (54).

Splenectomy

Splenic blood flow contributes to 25-30% of the total portal flow which may rise up to 50% in portal hypertension and plays a crucial role in portal overpressures following living donor liver transplantation and major hepatic resections. The role of splenectomy in portal flow modulation was first studied in rodent models (55). Splenectomy increases vascular compliance of graft, and hepatic serotonin levels which improve hepatic perfusion through its vasodilatory effect. Serotonin provides protection to the graft by increasing microcirculation and accelerates liver regeneration by stimulating endothelial cells to release vascular endothelial growth factor (56, 57). Simultaneous splenectomy reduced hypersplenism and prevented graft congestion from excessive portal flow in the first outcome report of six cases after left lobe living donor liver transplantation, and excluding splenectomy was an independent risk factor for SFSF in these patients (58). Patient survival rates were significantly higher in patients with a PVP ≤ 15 mm Hg than those with PVP ≥ 15mm Hg in a study by Kaoido et al. (59). Similarly, Kyoto group found that failure of

flow modulation (which they achieve with splenectomy) to maintain a PVP ≤ 15mm Hg is associated with SFSF syndrome and early graft loss (60).

The role of splenectomy in flow modulation and preventing SFSF syndrome is well described in LDLTs; however, its role in extended hepatectomies is only described in animal studies. Splenectomy significantly improved liver functions, and enhanced DNA synthesis and proliferation of cell nuclear antigens to facilitate liver regeneration in rats undergoing major hepatectomies (61). Similarly, Arakawa et al. reported reduced hepatocyte damage and improved survival after 90% hepatectomy with splenectomy in rats (55).

Splenic artery ligation

Splenic artery ligation was used in LDLT to prevent the risk of thrombocytopenia associated with splenectomy, however, later it was reported as an effective way to reduce the PVP and increase hepatic artery flow by Troisi et al. (62). Therefore, it is used as an alternate to splenectomy in reducing PVP and PVF. Shimada et al. showed that patients who underwent splenectomy after LDLT had better graft function and survival at one year (91.2% vs 77.9%) compared to splenic artery ligation, indicating the inferiority of later in flow modulation (63). Moon et al. described splenic devascularization as an alternative to splenectomy in selected LDLT recipients where SA and right gastro epiploic arteries and short gastric arteries were ligated and divided. In this small retrospective study, authors reported a better safety profile of this method (64).

Non-surgical ways for splenic artery ligation like splenic artery embolization have been described in small case series and case reports for flow modulation in LDLT showing promising results with less procedure related morbidity than (65). In context of PHLF, convincing data is still lacking to consider splenic artery ligation as a therapeutic option for flow modulation.

Portocaval shunts

The role of portocaval shunts in preventing SFSF from portal hyper-perfusion has been described for LDLTs. The decompression of portal system can prevent sinusoidal congestion and graft dysfunction in experimental models (66, 67). In clinical settings, hemi-portocaval shunts have shown better patient and graft survival (68). In a series of 13 patients undergoing adult to adult LDLT, Troisis et al. found a significant reduction of portal vein flow among the hemi-portocaval shunt group compared to the group without graft inflow modulation (190 ± 70 ml/min/100 g liver v/s 401 ± 225 ml/min/100 g liver; $p < 0.001$). It is important to note that excessive diversion of portal flow into systemic circulation can lead to steal syndrome which can cause graft ischemia. Therefore, Troisi et al. recommend measuring portal pressure and calibrating the size of shunt to avoid steal phenomenon (69). Given the similarity in underlying flow dynamics of LDLT grafts and remnant livers post hepatectomy, shunts can be an attractive future direction in preventing PHLF.

Pharmacological interventions

Although surgical techniques like splenectomy, splenic artery ligation and creation of shunts in animal models have shown promising results in portal flow modulation and decreasing the risks of PHLF, the procedure adds to the complexity of liver resection with associated morbidity. This led to the idea of exploring non-invasive options to reduce the portal venous flow and pressure using splanchnic vasoactive agents like octreotide, terlipressin and vasopressin. Historically, Tri-glycyl-lysine (terlipressin) has been used in cirrhotic patients to treat the complications of portal hypertension. Recent studies on pigs and rodents have shown marked reduction in portal venous flow and pressure and attenuation of liver injury after 80% and 90% hepatectomies (70). A study by Jo et al. demonstrated improved liver regeneration and survival with terlipressin in pigs following 90% hepatectomy with rapid and effective flow modulation (71). Similarly, due to its antioxidant and vasoconstrictor properties, somatostatin has been suggested as an experimental agent in reducing the risk of PHLF (70). Although the techniques for flow modulation have shown promising results in animal models and LDLTs, there role in reducing the risk of PHLF in clinical settings is still debatable and further studies are required to address this important issue.

Conclusion

In conclusion, the current review outlines the various strategies of volume and flow modulation that can be used in isolation or combination in the management of patients at risk of PHLF. PVE and PVL are well established methods of reducing PHLF in those with a small FLR. ALPPS and DVE show great promise at producing a larger, more rapid hypertrophy that may allow more patients to undergo potentially curative liver resection. Methods to modulate flow to the FLR are more established in liver transplantation, and in particular live donor liver transplant, but remain largely untested in the context of liver resection and mitigating PHLF.

Author contributions

RB and SB contributed equally and should be considered as first authors. BD: substantial contributions to the conception or design of the work; revising the draft, approval for publication.

RB: substantial contributions to the acquisition, analysis, or interpretation of data for the work drafting the work and provide approval for publication of the content. SB: substantial contributions to the acquisition, analysis, or interpretation of data for the work drafting the work and provide approval for publication of the content. RP: substantial contributions to the conception or design of the work; revising the draft, approval for publication. KT: substantial contributions to the conception or design of the work; revising the draft, approval for publication. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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