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Impact of postoperative morbidity on the prognosis of patients with hepatocellular carcinoma after laparoscopic liver resection: a multicenter observational study

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The long-term impact of postoperative morbidity following laparoscopic liver resection for hepatocellular carcinoma is unclear. This study aimed to investigate whether the prognosis of hepatocellular carcinoma patients were affected by postoperative morbidity after laparoscopic liver resection. Hepatocellular carcinoma patients who underwent curative-intent laparoscopic liver resection were included. Risk factors of 30-day morbidity were identified using logistic regression analysis. Early (≤ 2 years) and late (> 2 years) recurrence rates, overall survival, and time to recurrence were compared among patients with and without postoperative morbidity. Independent prognostic factors of overall survival and time to recurrence of these patients were investigated using Cox regression analysis. This study included 420 patients, 147 (35%) of whom experienced postoperative morbidity. Diabetes mellitus, cirrhosis, portal hypertension, Child-Pugh grade B, multiple tumors, poor tumor differentiation and intraoperative blood transfusion were risk factors of postoperative morbidity. Patients with postoperative morbidity had higher early and late recurrence rates than those without postoperative morbidity (38.8% vs. 22.4%, *P* = 0.001; 50% vs. 25.5%, *P* = 0.001). Postoperative morbidity was associated with decreased overall survival (median: 54.5 months vs. not reached, *P* < 0.001) and time to recurrence (median: 36.4 vs. 68.2 months; *P* < 0.001). Postoperative morbidity resulted in a 43% and 92% higher risk of long-term mortality (HR 1.43; 95% CI 1–2.03; *P* = 0.048) and recurrence (HR 1.92; 95% CI 1.41–2.62; *P* < 0.001). For hepatocellular carcinoma patients undergoing laparoscopic liver resection, long-term oncologic outcomes are adversely affected by postoperative morbidity. Therefore, it is of great importance for surgeons to prevent and manage postoperative morbidity.

Keywords Hepatocellular carcinoma, Laparoscopic liver resection, Morbidity, Survival, Recurrence

Hepatocellular carcinoma is the sixth most common cancer and the third leading cause of cancer-related death in the world[1]. Liver resection is the most effective treatment for patients with hepatocellular carcinoma who are eligible for surgery. In the past two decades, developments in surgical techniques and improvements in

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perioperative care have made hepatectomy safe for hepatocellular carcinoma, and some centers have decreased surgical mortality rates less than 3%[2–6]. Nevertheless, the incidence of postoperative morbidity remains high after hepatectomy[5–8]. Moreover, the oncologic outcomes of hepatocellular carcinoma patients following hepatectomy remain unsatisfactory due to high recurrence rates after surgery[9,10]. Currently, laparoscopic liver resection has gained wide acceptance among liver surgeons due to its advantages regarding minimal invasiveness, a shorter hospital stay, faster postoperative recovery and fewer postoperative morbidity[11–14]. To improve long-term survival of patients with hepatocellular carcinoma treated with hepatectomy, it is crucial to identify and manage risk factors for hepatocellular carcinoma recurrence so as to reduce their detrimental effects.

Postoperative morbidity has been proved to be associated with higher reoperation and re-admission rates, higher hospitalization costs, more hospital stays, and increased risk of early death after major surgery[15]. Postoperative morbidity is also demonstrated to be associated with increased tumor recurrence and decreased survival following surgery, including gastric, lung, pancreatic, biliary, colorectal and esophageal cancers[16–21]. The majority of previous studies were single-center studies or only examined the effect of early recurrence after surgery[3,6,22–24], raising questions about their validity and generalizability of the results. Moreover, in these studies, only deaths during hospitalization or within 30 days after surgery were excluded. Early postoperative mortality (≤ 90 days after surgery) was partially included, thereby underestimating the true short-term mortality attributable to postoperative morbidity.

In this observational cohort study, based on a large cohort of hepatocellular carcinoma patients treated with curative laparoscopic liver resection, we aimed to investigate whether postoperative morbidity affected long-term oncologic outcomes. Furthermore, independent risk factors for postoperative morbidity of hepatocellular carcinoma patients undergoing laparoscopic liver resection were identified.

Patients and methods

Patient selection

Patients who underwent curative-intent laparoscopic liver resection for hepatocellular carcinoma between January 2016 to December 2019 at one of four hospitals (Nantong First People's Hospital, Nantong Second People's Hospital, Chinese People's Liberation Army General Hospital, Zhongshan People's Hospital) were initially included in the study. The flowchart diagram of this study was shown in Fig. 1. The study was approved by the Institutional Review Board of Nantong First People's Hospital (approval number: 2024KT260). Due to the retrospective nature of the study, the Institutional Ethics Committee of Nantong First People's Hospital waived the need of obtaining informed consent.

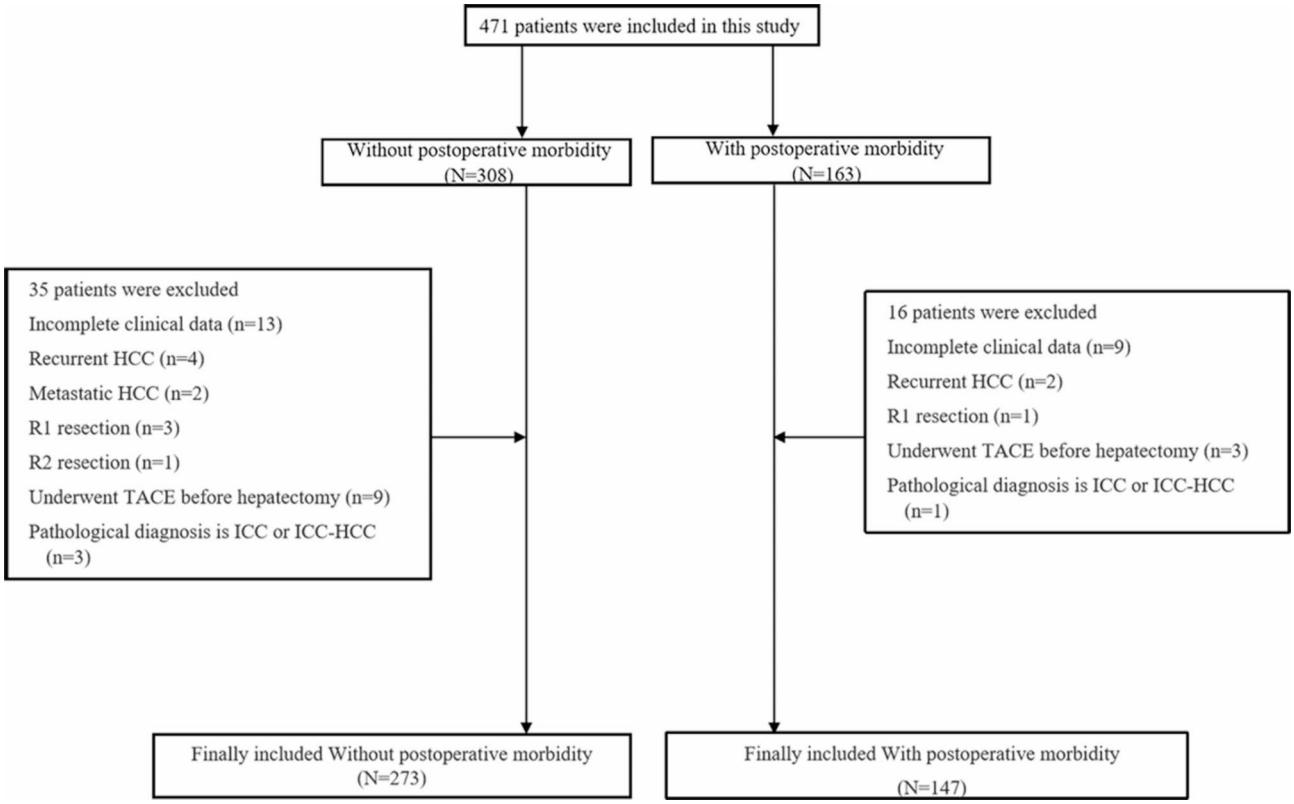

Fig. 1. The flow chart of this study. Abbreviation: HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; ICC, intrahepatic cholangiocarcinoma; ICC-HCC, intrahepatic cholangiocarcinoma-hepatocellular carcinoma.

The definition of curative laparoscopic liver resection was the removal of all microscopic and macroscopic tumors with a microscopically negative surgical margin. Patients with incomplete clinical data, recurrent or metastatic hepatocellular carcinoma, who underwent an R1 or R2 resection or received anti-cancer treatment before surgery, had intrahepatic cholangiocarcinoma or mixed intrahepatic cholangiocarcinoma-hepatocellular carcinoma, had lesions at Barcelona Clinic Liver Cancer stages C-D not feasible for laparoscopic liver resection, or had tumor recurrence within 90 days after surgery were excluded. Generally, each participating hospital adhered to the Guidelines for the Diagnosis and Treatment of Primary Liver Cancer when the decision of surgical resection was made for hepatocellular carcinoma[25]. A multidisciplinary treatment team consisted of surgeons, hepatologists, oncologists, radiologists, fully discussed to obtain a consensus about the treatment plan. Laparoscopic liver resection techniques were described in previous studies[10,26], and resection criteria remained constant throughout the study period.

Clinicopathological and operative variables

Several clinicopathological variables, such as age, sex, American Society of Anesthesiologists score, diabetes mellitus, body mass index, hepatitis B surface antigen, anti-hepatitis C virus, cirrhosis, portal hypertension, and Child-Pugh grade, were included in this study. body mass index over 30 was defined as obesity. Cirrhosis was confirmed by histopathological examination of the resected liver specimens. Portal hypertension was defined as esophageal varices and/or splenomegaly with a low platelet count (less than 100×10^9/L). The tumor-related variables were preoperative alpha-fetoprotein level, largest tumor size, tumor number, microvascular invasion, satellite nodules, tumor encapsulation and tumor differentiation. Surgery-related variables were intraoperative blood transfusion and blood loss, extent of hepatectomy, type of hepatectomy, and surgical resection margin. Major hepatectomy was defined as resection of equal to or more than three Couinaud liver segments, whereas minor hepatectomy was defined as resection of fewer than three segments. Anatomical and nonanatomical resections were defined according to the Brisbane 2000 Nomenclature of Liver Anatomy and Resections[27].

Perioperative outcomes

The 30- and 90-day mortality rates were recorded after surgery. The morbidity rates within 30 days after surgery were recorded and graded according to the Clavien-Dindo classification algorithm[28]. Postoperative morbidities, such as posthepatectomy liver failure, abdominal hemorrhage, bile leakage, pleural effusion, ascites, surgical site infection, respiratory infection, urinary tract infection, systemic sepsis, wound dehiscence, delayed gastric emptying, upper gastrointestinal bleeding, acute pancreatitis, deep venous thrombosis, were included in our study. Postoperative hepatic failure was defined according to the "50–50 criteria" on or after postoperative day 5[29]. The definition of intra-abdominal hemorrhage was a drop of hemoglobin level > 3 g/dL compared to the baseline level before liver resection, any postoperative transfusion of packed red blood cells, or invasive reintervention. Bile leakage was defined as a bilirubin concentration of the abdominal drainage fluid threefold greater than that in the serum. Postoperative morbidities such as pleural effusions and ascites needing diuretics or paracentesis were also included. Surgical site infection was classified as incisional infection (superficial or deep) and organ/space infection[30].

Patient follow-up

All patients were regularly followed up in each hospital's outpatient clinic. Every participating hospital used a consistent postoperative follow-up program which consisted of serum alpha-fetoprotein level, ultrasonography, computed tomography and magnetic resonance imaging at a 2–3 month interval for the first 6 months, followed by 3–4 month interval for the next 18 months, and then 3–6 months once thereafter. Tumor recurrence was monitored and confirmed by contrast-enhanced computed tomography or magnetic resonance imaging, which manifested as the appearance of new intrahepatic or extrahepatic lesions along with or without an increase in serum alpha-fetoprotein levels. Using 2 years as the cut-off, we divided tumor recurrence into early and late recurrence. Overall survival and time to recurrence were the primary endpoints; early and late recurrence rates were the secondary endpoints. Overall survival is calculated as the duration from the time of laparoscopic liver resection to the date of death or the last follow-up. Time to recurrence was defined as the time from the date of laparoscopic liver resection to the date of the first tumor recurrence or the last follow-up.

Statistical analysis

Continuous variables and categorical variables were expressed as mean (standard deviation) or median (interquartile range), and number (percentage), respectively. Chi-square test or Fisher's exact test was used to compare categorical variables. Student's t-test or Mann-Whitney U test was used to compare continuous variables. Patients with postoperative deaths within 90 days of laparoscopic liver resection were excluded from survival analysis in order to minimize the effects of early deaths on long-term survival. Overall survival and time to recurrence were plotted using the Kaplan-Meier method and compared using the log-rank test. In order to identify independent risk factors for overall survival and time to recurrence, univariable and multivariable Cox regression analyses were conducted. Multivariable Cox regression analysis was conducted based on variables with $P < 0.1$ in univariable analyses using a forward stepwise selection process. Risk factors of postoperative morbidity were identified using binary logistic regression analysis. The significance level was set as two-tailed P values less than 0.05 across the study. SPSS software version 25.0 (SPSS, Chicago, IL, USA) was used for statistical analysis.

Results

Patient characteristics

In patients with or without postoperative morbidity, several differences in clinicopathological and operative characteristics were noted (Table 1). The proportion of patients with Child-Pugh grade B, preoperative alpha-fetoprotein > 400 μg/L, largest tumor size > 5 cm, intraoperative blood transfusion, and resection margin < 1 cm were significantly higher in patients with postoperative morbidity compared with patients without postoperative morbidity (all $P < 0.05$). The other clinicopathological and operative characteristics were balanced between the two groups.

Perioperative outcomes

In Table 2, perioperative short-term outcomes of the 420 patients are summarized. Among the patients who died within 30 days and 90 days after surgery, 5 (1.19%) and 13 (3.1%) patients experienced postoperative mortality, respectively. 147 (35%) patients had postoperative 30-day morbidity, among whom 55 (13.1%) and 92 (21.9%) had major and minor morbidities, respectively. The top three types of morbidity were pleural effusion (15.5%), surgical site infection (9.52%) and ascites (6.67%).

Risk factors of postoperative morbidity

Diabetes mellitus (OR: 9.81; 95% CI 4.14–24.5; $P < 0.001$), cirrhosis (OR: 2.45; 95% CI 1.33–4.73; $P = 0.005$), portal hypertension (OR: 2.27; 95% CI 1.22–4.16; $P = 0.008$), Child-Pugh grade B (OR: 2.76; 95% CI 1.35–5.59; $P = 0.005$), multiple tumors (OR: 2.18; 95% CI 1.17–4.01; $P = 0.013$), poor tumor differentiation (OR: 1.98; 95% CI 1.11–3.64; $P = 0.023$) and intraoperative blood transfusion (OR: 2.3; 95% CI 1.29–4.1; $P = 0.005$) were identified as independent risk factors for postoperative morbidity of hepatocellular carcinoma patients undergoing laparoscopic liver resection (Table 3).

Long-term survival outcomes

After excluding 13 patients who died within 90 days postoperatively, the long-term survival outcomes of the 407 patients who underwent curative laparoscopic liver resection for hepatocellular carcinoma were stratified according to presence of absence of postoperative morbidity (Table 4). Following a median follow-up duration of 41.8 months, deaths and tumor recurrences occurred in 56.8% (79/139) and 65.4% (91/139) in patients with postoperative morbidity, and in 27.6% (74/268) and 39.9% (107/268) in patients without postoperative morbidity (both $P < 0.001$). The early recurrence rate (38.8%, 54/139) among patients with postoperative morbidity was

Variables	Without postoperative morbidity ($N = 273$)	With postoperative morbidity ($N = 147$)	P
Age > 60 years	53 (19.4%)	34 (23.1%)	0.441
Male sex	226 (82.8%)	126 (85.7%)	0.523
ASA score > 2	34 (12.5%)	24 (16.3%)	0.343
Diabetes mellitus	16 (5.86%)	17 (11.6%)	0.060
Obesity	10 (3.66%)	11 (7.48%)	0.139
Anti-HCV (+)	15 (5.49%)	8 (5.44%)	1.000
HBsAg (+)	242 (88.6%)	134 (91.2%)	0.526
Cirrhosis	190 (69.6%)	85 (57.8%)	0.021
Portal hypertension	50 (18.3%)	38 (25.9%)	0.092
Child-Pugh grade B	27 (9.89%)	27 (18.4%)	0.020
Preoperative AFP > 400 μg/L	93 (34.1%)	69 (46.9%)	0.013
Largest tumor size > 5 cm	128 (46.9%)	97 (66.0%)	< 0.001
Multiple tumors	51 (18.7%)	34 (23.1%)	0.340
Microvascular invasion	112 (41.0%)	66 (44.9%)	0.508
Satellite nodules	64 (23.4%)	34 (23.1%)	1.000
Incomplete encapsulation	135 (49.5%)	83 (56.5%)	0.204
Poor tumor differentiation	154 (56.4%)	90 (61.2%)	0.395
Intraoperative blood loss, ml[a]	300 (100, 400)	400 (100, 650)	0.308
Intraoperative blood loss > 400 ml	59 (21.6%)	44 (29.9%)	0.076
Intraoperative blood transfusion	48 (17.6%)	59 (40.1%)	< 0.001
Major hepatectomy	56 (20.5%)	39 (26.5%)	0.199
Non-anatomical hepatectomy	75 (27.5%)	29 (19.7%)	0.102
Resection margin < 1 cm	118 (43.2%)	91 (61.9%)	< 0.001
BCLC stage B	32 (11.7%)	23 (15.6%)	0.255

Table 1. Comparisons of patients' clinicopathologic and operative variables between patients with and without postoperative morbidity. ASA: American Society of Anesthesiologists, HBsAg: hepatitis B surface antigen, HCV: hepatitis C virus, AFP: alpha-fetoprotein, BCLC: Barcelona Clinic Liver Cancer. [a] Values are median (interquartile range).

Perioperative outcomes ($N=420$)	Patients n (%)
Postoperative 30-day morbidity	147 (35%)
Minor morbidity (Clavien-Dindo grade I-II)	92 (21.9%)
Major morbidity (Clavien-Dindo grade III-V)	55 (13.1%)
Types of postoperative 30-day morbidity	
Post-hepatectomy liver failure	24 (5.71%)
Abdominal hemorrhage	5 (1.19%)
Bile leak	10 (2.38%)
Pleural effusion	65 (15.5%)
Ascites	28 (6.67%)
Surgical site infection	40 (9.52%)
Respiratory infection	12 (2.86%)
Urinary tract infection	6 (1.43%)
Systemic sepsis	12 (2.86%)
Wound dehiscence	5 (1.19%)
Delayed gastric emptying	4 (0.95%)
Upper gastrointestinal bleeding	3 (0.71%)
Acute pancreatitis	3 (0.71%)
Deep venous thrombosis/thrombophlebitis	4 (0.95%)
Others	6 (1.43%)
Postoperative 30-day mortality	5 (1.19%)
Postoperative 90-day mortality	13 (3.1%)
Postoperative acute liver and/or renal failure	3/13 (23.1%)
Fast recurrence and tumor progression	4/13 (30.8%)
Postoperative infectious complications	3/13 (23.1%)
Abdominal hemorrhage	1/13 (7.7%)
Upper gastrointestinal hemorrhage	1/13 (7.7%)
Cardiovascular and cerebrovascular accident	1/13 (7.7%)
Postoperative hospital stay, days[a]	11 (10, 15)

Table 2. Postoperative outcomes of 420 patients undergoing curative laparoscopic hepatectomy for hepatocellular carcinoma. [a] Values are median (interquartile range).

significantly higher than that among patients without postoperative morbidity (22.4%, 60/268, $P<0.001$). Also, the late recurrence rate was significantly higher among patients with postoperative morbidity (50%, 37/74) than those without postoperative morbidity (25.5%, 47/184, $P<0.001$). As shown in Fig. 2A and B, the median overall survival and time to recurrence of patients with postoperative morbidity were worse than those without postoperative morbidity (54.5 months vs. not reached, and 36.4 vs. 68.2 months, both $P<0.001$). As shown in Fig. 2C and D, patients with postoperative morbidity had significantly higher cumulative early and late recurrence rates compared with those without postoperative morbidity ($P<0.001$ and $P=0.014$, respectively).

Prognostic analyses for overall survival and time to recurrence

Independent risk factors associated with overall survival of these hepatocellular carcinoma patients were portal hypertension ($P=0.003$), Child-Pugh grade B ($P<0.001$), largest tumor size > 5 cm ($P<0.001$), microvascular invasion ($P<0.001$), intraoperative blood transfusion ($P=0.038$), major hepatectomy ($P=0.001$), resection margin < 1 cm ($P=0.033$) and postoperative morbidity ($P=0.048$) (Table 5). Independent risk factors associated with time to recurrence of these hepatocellular carcinoma patients were Child-Pugh grade B ($P=0.003$), largest tumor size > 5 cm ($P=0.010$), microvascular invasion ($P=0.021$), intraoperative blood transfusion ($P=0.023$), major hepatectomy ($P=0.029$), resection margin < 1 cm ($P=0.039$) and postoperative morbidity ($P<0.001$) (Table 6). Postoperative morbidity was associated with a 43% higher risk of mortality as well as a 92% higher risk of recurrence.

Discussion

During the past decade, the number of minimally invasive liver resection performed worldwide has increased rapidly. The introduction of new surgical equipment and increased experience in laparoscopic liver resection have allowed this procedure to be performed more frequently than before. The maturity and indication of laparoscopic liver resection have rapidly developed, making it as a safe alternative to open liver resection.

In the field of surgery, defining and measuring surgical quality has been challenging, whether they pertain to systems, processes, or outcomes[15]. Postoperative morbidity has gained increasing attention in clinical practice as a cancer-specific quality measure. In light of the fact that some types of postoperative morbidity may be preventable or controllable, it is crucial to investigate the possible association between postoperative morbidity

Variables	UV OR (95% CI)	UV *P*	MV OR (95% CI)	MV *P*
Age > 60 years	1.45 (0.82–2.50)	0.19		
Male sex	0.79 (0.43–1.51)	0.461		
ASA score > 2	2.40 (1.30–4.37)	**0.004**	NS	NS
Diabetes mellitus	12.1 (5.61–27.7)	**< 0.001**	9.81 (4.14–24.5)	**< 0.001**
Obesity	2.57 (0.99–6.33)	**0.043**	NS	NS
Anti-HCV (+)	0.82 (0.23–2.26)	0.727		
HBsAg (+)	0.74 (0.36–1.59)	0.407		
Cirrhosis	2.27 (1.32–4.10)	**0.004**	2.45 (1.33–4.73)	**0.005**
Portal hypertension	3.23 (1.91–5.45)	**< 0.001**	2.27 (1.22–4.16)	**0.008**
Child-Pugh grade B	3.64 (1.97–6.65)	**< 0.001**	2.76 (1.35–5.59)	**0.005**
Preoperative AFP > 400 μg/L	1.97 (1.22–3.20)	**0.006**	NS	NS
Largest tumor size > 5 cm	1.31 (0.81–2.13)	0.278		
Multiple tumors	2.22 (1.29–3.79)	**0.004**	2.18 (1.17–4.01)	**0.013**
Microvascular invasion	0.83 (0.51–1.35)	0.458		
Satellite nodules	1.29 (0.74–2.19)	0.364		
Incomplete encapsulation	1.51 (0.93–2.46)	0.096		
Poor tumor differentiation	1.97 (1.19–3.34)	**0.010**	1.98 (1.11–3.64)	**0.023**
Intraoperative blood loss > 400 ml	1.10 (0.62–1.87)	0.744		
Intraoperative blood transfusion	2.39 (1.44–3.96)	**< 0.001**	2.30 (1.29–4.10)	**0.005**
Major hepatectomy	1.07 (0.60–1.85)	0.822		
Non-anatomical hepatectomy	1.00 (0.56–1.71)	0.989		
Resection margin < 1 cm	1.58 (0.98–2.58)	0.063		
BCLC stage B	1.27 (0.66–2.43)	0.477		

Table 3. Univariable and multivariable logistic regression analyses of risk factors associated with postoperative morbidity following laparoscopic hepatectomy for hepatocellular carcinoma. ASA: American Society of Anesthesiologists, HBsAg: hepatitis B surface antigen, HCV: hepatitis C virus, AFP: alpha-fetoprotein, BCLC: Barcelona Clinic Liver Cancer, OR: Odds ratio, MV: multivariable, NS: Not significant, UV: univariable, CI: Confidence interval.

Long-term outcomes	Total (*N* = 407)	Without postoperative morbidity (*N* = 268)	With postoperative morbidity (*N* = 139)	*P*
Period of follow-up, months [a]	41.8 (24.4, 63.9)	42.9 (26.4, 64.2)	38.4 (20.3, 63.8)	0.136
Recurrence at the follow-up	198 (48.6%)	107 (39.9%)	91 (65.4%)	< 0.001
Early recurrence (≤ 2 years)	114 (28%)	60 (22.4%)	54 (38.8%)	< 0.001
Late recurrence (> 2 years) [b]	84 (32.6%)	47 (25.5%)	37 (50%)	< 0.001
Death during the follow-up	153 (37.6%)	74 (27.6%)	79 (56.8%)	< 0.001
Median OS, 95% CI, months	69.8, 65.5-NA	NA, 72.2-NA	54.5, 47.8–65.5	< 0.001
1-year OS rate, %	93.9	96.2	89.8	
3-year OS rate, %	78.9	83.9	69.8	
5-year OS rate, %	59.5	67.3	46.1	
Median TTR, 95% CI, months	55.2, 42.7–65.6	68.2, 56.8-NA	36.4, 26-45.5	< 0.001
1-year TTR rate, %	84.3	87.9	77.9	
3-year TTR rate, %	60.8	66.8	50	
5-year TTR rate, %	46.3	53.6	33.7	

Table 4. Comparisons of long-term outcomes between patients with and without postoperative morbidity after excluding postoperative early deaths (≤ 90 days after surgery). CI: confidence interval; OS, overall survival; TTR, time to recurrence; NA, not accessible. [a] Values are median (quartile range). [b] The denominator represents the number of patients who were recurrence-free and alive at 2 years after surgery.

and long-term oncological outcomes after surgery. The postoperative morbidity can be used not only to assess the quality and safety of perioperative care, but also as a modifiable predictor of long-term outcomes. A better outcome for hepatocellular carcinoma patients treated with laparoscopic liver resection may be achieved by figuring out ways to intervene and remedy postoperative morbidity.

This study was designed to find out whether postoperative morbidity could affect long-term oncologic outcome of hepatocellular carcinoma patients following curative laparoscopic liver resection. After adjusting

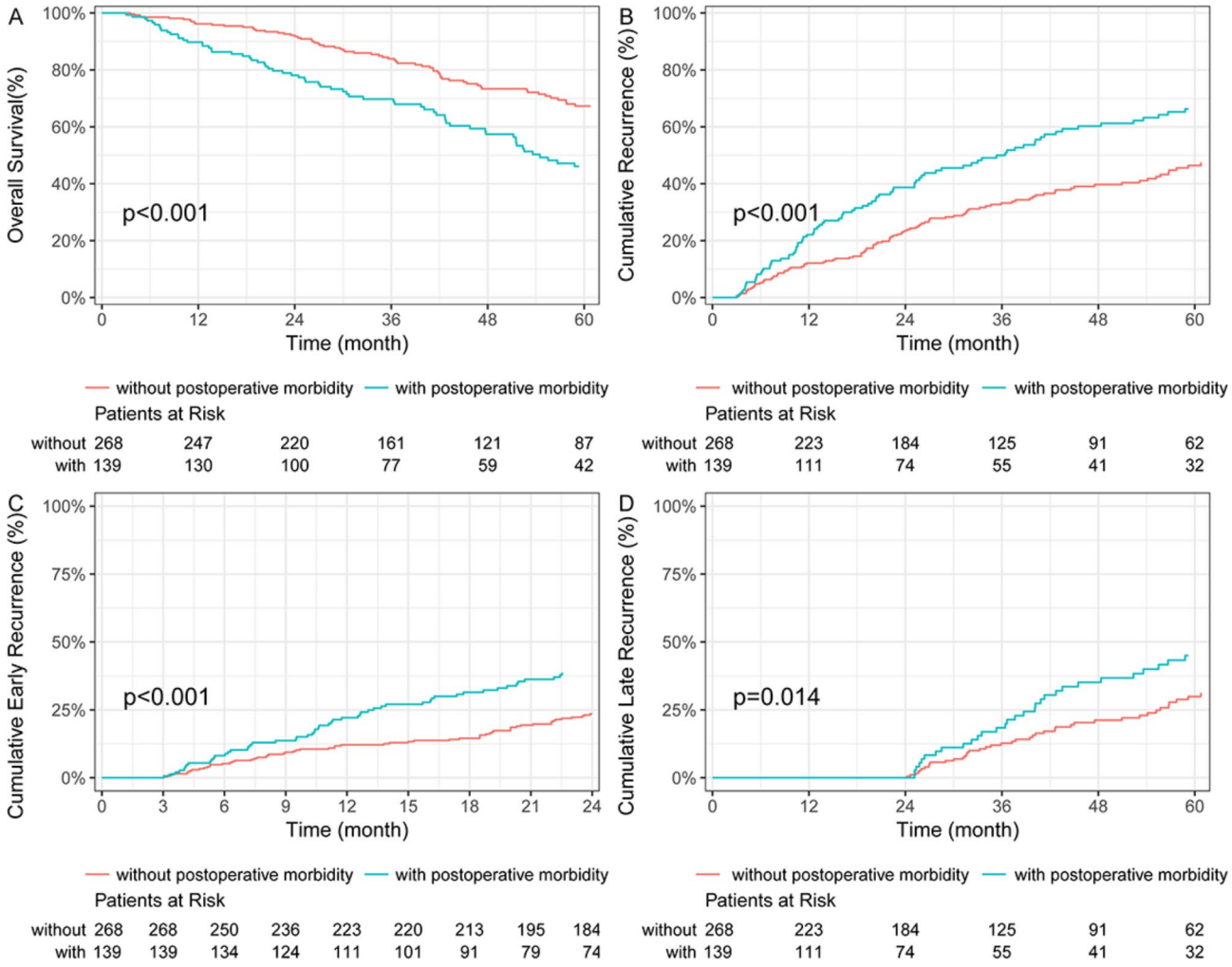

Fig. 2. Cumulative incidence of overall survival (**A**) and recurrence (**B**) curves comparisons and early recurrence (≤ 2 years after surgery) (**C**) and late recurrence (> 2 years after surgery) (**D**) curves comparisons between patients with and without postoperative 30-day morbidity.

for competing clinicopathological variables, postoperative morbidity was also associated with lower survival and increased recurrence. Based on the results, it is evident that postoperative morbidity adversely affects the prognosis of hepatocellular carcinoma patients after laparoscopic liver resection.

At high volume and experienced centers, perioperative mortality and morbidity after curative hepatectomy are reported to be 0-5% and 20-70%, respectively[3,5,6,8,31–33]. In the present study, 30-day mortality and morbidity rates were 1.19% and 35%, respectively. In previous studies, survival analysis investigating postoperative morbidity only excluded patients who deceased within 30 days of surgery, but did not exclude patients who died between 30 and 90 days[3,6,22,23,34]. Our study examined the association of postoperative morbidity with long-term survival of hepatocellular carcinoma patients after excluding patients who died within postoperative 90 days. Because of the accurate definition of postoperative 30-day morbidity, the multicenter study design, the large sample size, and the exclusion of early deaths from prognostic analyses, the current study was methodologically robust to draw convincing findings.

In our study, some significant differences were found among patients with and without 30-day morbidity following surgery. Previous studies used the propensity score matching method to examine the association between postoperative morbidity and patients' prognosis with the aim of balancing baseline characteristics[35,36]. If not used appropriately, this statistical approach could increase the selection bias between the groups. The variable of postoperative morbidity may not be appropriate to use for propensity matching since it is already an existed outcome following surgery. Classical statistical analytical methods, such as univariable and multivariable Cox regression model, are more applicable and practicable in this circumstance.

To decrease postoperative morbidity rate, it is necessary to understand relevant risk factors. In the present study, diabetes mellitus, cirrhosis, portal hypertension, Child-Pugh grade B, multiple tumors, poor tumor differentiation and intraoperative blood transfusion were identified as risk factors of postoperative morbidity. The results informed us of important clinical guiding implications. First, diabetics, cirrhotic patients, or patients with poor liver function should be given special attention to the possibility of postoperative morbidity, including

Variables	UV HR (95% CI)	UV *P*	MV HR (95% CI)	MV *P*
Age > 60 years	0.99 (0.68–1.46)	0.976		
Male sex	1.44 (0.89–2.32)	0.14		
ASA score > 2	1.47 (0.98–2.20)	0.062		
Diabetes mellitus	1.69 (1.05–2.70)	**0.03**	NS	NS
Obesity	1.91 (1.06–3.45)	**0.031**	NS	NS
Anti-HCV (+)	1.31 (0.67–2.57)	0.432		
HBsAg (+)	1.14 (0.68–1.91)	0.62		
Cirrhosis	1.34 (0.94–1.91)	0.1		
Portal hypertension	2.13 (1.53–2.97)	**< 0.001**	1.71 (1.20–2.42)	**0.003**
Child-Pugh grade B	2.22 (1.52–3.24)	**< 0.001**	2.08 (1.39–3.10)	**< 0.001**
Preoperative AFP > 400 μg/L	1.61 (1.17–2.22)	**0.003**	NS	NS
Largest tumor size > 5 cm	2.32 (1.63–3.29)	**< 0.001**	2.04 (1.43–2.92)	**< 0.001**
Multiple tumors	1.63 (1.14–2.34)	**0.007**	NS	NS
Microvascular invasion	1.98 (1.44–2.73)	**< 0.001**	1.95 (1.40–2.71)	**< 0.001**
Satellite nodules	1.34 (0.95–1.89)	0.090		
Incomplete encapsulation	1.38 (0.99–1.91)	0.055		
Poor tumor differentiation	1.47 (1.04–2.09)	**0.029**	NS	NS
Intraoperative blood loss > 400 ml	1.53 (1.08–2.16)	**0.017**	NS	NS
Intraoperative blood transfusion	1.91 (1.38–2.66)	**< 0.001**	1.44 (1.02–2.03)	**0.038**
Major hepatectomy	1.45 (1.02–2.05)	**0.037**	1.79 (1.25–2.57)	**0.001**
Non-anatomical hepatectomy	0.86 (0.59–1.26)	0.444		
Resection margin < 1 cm	1.66 (1.20–2.31)	**0.002**	1.45 (1.03–2.05)	**0.033**
BCLC stage B	1.59 (0.93–2.72)	0.091		
Postoperative morbidity	2.1 (1.52–2.91)	**< 0.001**	1.43 (1.00–2.03)	**0.048**

Table 5. Univariable and multivariable Cox-regression analyses of risk factors associated with overall survival following laparoscopic hepatectomy for hepatocellular carcinoma. ASA: American Society of Anesthesiologists, HBsAg: hepatitis B surface antigen, HCV: hepatitis C virus, AFP: alpha-fetoprotein, BCLC: Barcelona Clinic Liver Cancer, HR: Hazard ratio, MV: multivariable, NS: Not significant, UV: univariable, CI: Confidence interval.

surgical site infection, posthepatectomy liver failure, and other infectious complications. For these high-risk patients, it may be worthwhile to extend the duration of antibiotic use. Second, in terms of surgical technique, reducing intraoperative blood loss and avoiding intraoperative blood transfusion should be achieved as far as possible.

Based on the time to recurrence after surgery, hepatocellular carcinoma recurrence can be divided into early and late recurrences, generally using 2 years as a threshold[9,37]. Early recurrence is commonly attributable to occult metastases from the primary tumor and are associated with primary tumor characteristics such as large tumor size, multiple nodules, vascular invasion and satellite lesions[38,39]. Conversely, late recurrence often has a clonal origin that differs from the original tumor, suggesting a second tumor in the remnant liver. From this perspective, late recurrence is related to host factors, including sex, cirrhosis, and hepatitis status[10,40]. It has been reported that postoperative morbidity is closely associated with early recurrence following curative hepatectomy for hepatocellular carcinoma[22]. However, no study has yet found a link between postoperative morbidity and late recurrence. This study revealed that among the patients who were recurrence-free and alive at 2 years of surgery, patients who had postoperative morbidity had significantly higher cumulative late recurrence rates than patients who did not have postoperative morbidity. To the best of our knowledge, this is the first study that illustrates the association between postoperative morbidity and late recurrence after laparoscopic liver resection for hepatocellular carcinoma. Consequently, some enforceable measures can be undertaken to reduce postoperative morbidity following laparoscopic liver resection for hepatocellular carcinoma.

Similar to the immunosuppressive effects of blood transfusions[41], it is suggested that postoperative morbidity also has immunomodulatory effects. Evidence shows that major surgery can trigger an inflammation response characterized by high levels of inflammatory cytokines such as interleukin-1 and interleukin-6[42–44]. Postoperative morbidity may prolong the inflammatory response and maintain immunosuppressive status, which accelerates tumor metastasis by increasing the adhesion of circulating tumor cells[42,45,46]. Furthermore, postoperative stress response can suppress cell-mediated immune function. Therefore, residual malignant cells may progress and metastasize rapidly during the immunosuppressive periods[45]. However, the potential association between postoperative morbidity and oncological outcome and its underlying mechanism need further research.

The present study had several limitations. First, since this study was retrospective, it had inherent bias, and variables such as future liver remnant and preoperative indocyanine green are not taken into account. Second, because the study was multicenter, the surgical expertise of surgeons and the quality of perioperative care could be heterogeneous in different centers. Third, most patients in this study were infected with hepatitis B virus. In

Variables	UV HR (95% CI)	UV *P*	MV HR (95% CI)	MV *P*
Age > 60 years	1.01 (0.72–1.41)	0.97		
Male sex	1.32 (0.89–1.97)	0.17		
ASA score > 2	1.44 (1.00–2.05)	**0.047**	NS	NS
Diabetes mellitus	1.84 (1.23–2.77)	**0.003**	NS	NS
Obesity	1.69 (0.96–2.97)	0.067		
Anti-HCV (+)	1.27 (0.69–2.34)	0.436		
HBsAg (+)	1.23 (0.76–1.99)	0.408		
Cirrhosis	1.42 (1.04–1.93)	**0.028**	NS	NS
Portal hypertension	1.29 (0.94–1.77)	0.122		
Child-Pugh grade B	2.03 (1.44–2.88)	< **0.001**	1.76 (1.22–2.53)	**0.003**
Preoperative AFP > 400 μg/L	1.41 (1.07–1.86)	**0.016**	NS	NS
Largest tumor size > 5 cm	1.61 (1.21–2.15)	**0.001**	1.47 (1.10–1.96)	**0.010**
Multiple tumors	1.66 (1.21–2.27)	**0.002**	NS	NS
Microvascular invasion	1.44 (1.09–1.92)	**0.011**	1.41 (1.05–1.89)	**0.021**
Satellite nodules	1.29 (0.95–1.75)	0.103		
Incomplete encapsulation	1.32 (1.00–1.76)	0.052		
Poor tumor differentiation	1.35 (1.01–1.82)	**0.046**	NS	NS
Intraoperative blood loss > 400 ml	1.40 (1.03–1.91)	**0.034**	NS	NS
Intraoperative blood transfusion	1.86 (1.39–2.49)	< **0.001**	1.43 (1.05–1.95)	**0.023**
Major hepatectomy	1.37 (1.00–1.88)	**0.048**	1.43 (1.04–1.96)	**0.029**
Non-anatomical hepatectomy	0.75 (0.53–1.05)	0.092		
Resection margin < 1 cm	1.53 (1.15–2.02)	**0.003**	1.37 (1.02–1.85)	**0.039**
BCLC stage B	1.32 (0.87–2.02)	0.194		
Postoperative morbidity	2.53 (1.90–3.36)	< **0.001**	1.92 (1.41–2.62)	< **0.001**

Table 6. Univariable and multivariable Cox-regression analyses of risk factors associated with time-to-recurrence following laparoscopic hepatectomy for hepatocellular carcinoma. ASA: American Society of Anesthesiologists, HBsAg: hepatitis B surface antigen, HCV: hepatitis C virus, AFP: alpha-fetoprotein, BCLC: Barcelona Clinic Liver Cancer, HR: Hazard ratio, MV: multivariable, NS: Not significant, UV: univariable, CI: Confidence interval.

order to ensure a generalizable finding, the study must be externally validated in a Western cohort. Last, robotic hepatectomy has been shown to render a lower postoperative morbidity than laparoscopic liver resection. Consequently, different surgical approaches may have various effects on postoperative morbidity and long-term prognoses, which needs further studies.

Conclusion

This large-scale, multicenter observational study concluded that postoperative morbidity reduces long-term survival and increases recurrence among patients undergoing curative laparoscopic liver resection for hepatocellular carcinoma. Independent risk factors associated with postoperative morbidity included diabetes mellitus, cirrhosis, portal hypertension, Child-Pugh grade B, multiple tumors, poor tumor differentiation and intraoperative blood transfusion. To improve long-term oncologic outcomes of hepatocellular carcinoma patients following laparoscopic liver resection, additional efforts should be made on optimization of preoperative assessment, surgical techniques and perioperative care, in order to reduce postoperative morbidity.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

Conception and design: S.Y., H.Z. and Z.M.; Administrative support: S.Y., H.Z. and Z.M.; Provision of study materials or patients: H.Z., H.N., A.Z., J.Z.; Collection and assembly of data: S.Y., H.N., A.Z., J.Z.; Data analysis and interpretation: S.Y., H.N., A.Z., J.Z.; Statistical analysis: S.Y., H.N., A.Z., J.Z.; Manuscript writing: All authors; Final approval of manuscript: All authors.

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Declarations

Competing interests

The authors declare no competing interests.

Consent to participate

This study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Ethical approval was obtained from the Institutional Ethics Committee of Nantong First People's Hospital (approval number: 2024KT260). Due to the retrospective nature of the study, the Institutional Ethics Committee of Nantong First People's Hospital waived the need of obtaining informed consent.

Consent to publish

All authors confirm that the work described has not been published before and is not under consideration for publication elsewhere. All authors have seen and gave consent to the publication of this study.

Ethics approval

Ethical approval was obtained from the Institutional Ethics Committee of Nantong First People's Hospital (approval number: 2024KT260). Due to the retrospective nature of the study, the Institutional Ethics Committee of Nantong First People's Hospital waived the need of obtaining informed consent.

Additional information

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