



Laparoscopic hepatectomy for hepatocellular carcinoma: short- and long-term outcomes with blood loss

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Background: Laparoscopic hepatectomy (LH) for treating hepatocellular carcinoma (HCC) is a complex procedure. Compared to open hepatectomy (OH), LH offers certain advantages such as faster recovery, smaller incisions, and shorter hospital stay, but bleeding during LH remains a significant concern. Currently, the impacts of blood loss on the short- and long-term outcomes of patients undergoing LH are poorly understood. This retrospective study analyzes the impacts of blood loss on the prognosis of LH in HCC patients.

Methods: Between 2001 and 2019, 192 patients underwent LH for HCC at a single high-volume center. These patients were divided into two groups according to intraoperative blood loss (IBL) (Group A: ≤ 250 mL; Group B: > 250 mL). The patient characteristics assessed included age, gender, cirrhosis, hepatitis B virus (HBV) infection, Child-Pugh class, number of tumors, tumor size, vascular invasion, and diabetes mellitus. The perioperative and postoperative factors compared included operative time, blood loss, type of resection, blood transfusion, general complications, surgical complications, hospital mortality, and postoperative hospital stay.

Results: Factors associated with IBL in our multivariate analysis included the type of resection ($P < 0.01$) and operative time ($P < 0.01$). IBL, tumor size and number of tumors were independent predictors of a patient's overall survival (OS) and recurrence-free survival (RFS). Through our subgroup multivariate analysis, we found that IBL was the only significant factor associated with RFS ($P < 0.02$). There was also a noted IBL "dose effect", as patients with IBL $> 1,000$ mL had a worse median OS (24 months) and median RFS (6 months), while patients with IBL 250–1,000 mL had a median OS of 36 months and RFS of 12 months, and patients with IBL ≤ 250 mL had a median OS of 36 months and RFS of 24 months.

Conclusions: We found that the extent of IBL during LH was related to tumor size, operative time, and surgery type. Increased IBL during LH was also an independent prognostic factor for tumor recurrence. Furthermore, a dose-response relationship between increased IBL and decreased RFS and OS was evident.

Keywords: Laparoscopic hepatectomy (LH); hepatocellular carcinoma (HCC); intraoperative blood loss (IBL); retrospective study; postoperative outcomes

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Introduction

In 2019, more than half of the world's liver cancer (LC) cases occurred in China. 80% of these cases were found to be at intermediate and advanced stages because of the high prevalence of hepatitis B virus (HBV) infection (1,2). Surgical resection is still an effective treatment for advanced LC; however, laparoscopic hepatectomy (LH) is becoming a common procedure in treating hepatocellular carcinoma (HCC). This is due to the widespread dissemination of laparoscopic technology (3) since the First International Consensus Conference on Laparoscopic Liver Resection in 2008 (4).

However, serious postoperative complications such as poor liver function combined with major surgical trauma are still prevalent among patients. Risk factors for complications related to open hepatectomy (OH) include blood loss (5-9) type of resection (10), presence of comorbidity, HBV infection, cirrhosis (11), serum albumin levels (6), Child-Pugh class, blood transfusion (12), anesthesia, and operative time (7). Previous studies have reported that intraoperative blood loss (IBL) can significantly affect the complication rate of laparoscopic LC surgery (5,8). Compared to OH, LH is more effective in terms of its impact on hospital stay, blood loss, and the complication rate (13-15). In colorectal cancer (16) and endometrial cancer (17) surgery, laparoscopic surgery also has the advantage of reducing blood loss. However, the laparoscopic surgical approach is more challenging; thus, few studies have elaborated on the independent impact it has on blood loss and the short- (8) and long-term outcomes of patients undergoing LH for HCC.

For this reason, our study analyzed 192 HCC patients who underwent LH to assess the impacts LH has on blood loss and short- and long-term outcomes. The findings of this study can be used to encourage surgeons to reduce the amount of bleeding during LH and enable surgeons and anesthesiologists to rationally use blood products based on the amount of IBL, thereby preventing patients from unfavorable prognostic risk factors during and after surgery.

We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/tcr-21-463>).

Methods

Study group

The data of consecutive patients who underwent LH for

HCC from 2001 to 2019 at the Sir Run Run Shaw Hospital in Hangzhou, China, were retrieved retrospectively. Follow-up data were obtained from our material database and through direct contact via phone with patients and their families. There were 203 patients diagnosed with HCC and who underwent LH. However, we were unable to follow up with 9 of these patients due to incorrect contact information. This left a total of 192 HCC patients for our study. *Table 1* displays the baseline characteristics of these remaining patients, while *Table 2* lists the patients' surgical characteristics and surgical outcomes. Based on previously published reports on OH (8,18,19), the median IBL of HCC patients who underwent LH was 250 (range: 5–5,000) mL.

For this reason, we divided the patients in our study into two groups: the first was for those with an IBL less than 250 mL (Group A: n=97), and the second was for those with an IBL of more than 250 mL (Group B: n=95). These two groups were then compared in terms of tumor characteristics, type of surgery, and prognosis. To better verify the impact of high levels of blood loss, we analyzed the correlation between different levels of blood loss and a patient's overall survival (OS) and recurrence-free survival (RFS).

The patient characteristics assessed included age, gender, cirrhosis, HBV infection, Child-Pugh class, number of tumors, tumor size, vascular invasion, and diabetes mellitus (*Table 1*). Perioperative and postoperative factors were compared, including the operative time, blood loss, type of resection, blood transfusion, general complications, surgical complications, hospital mortality, and postoperative hospital stay (*Table 2*).

Surgical procedures

The same experienced surgical team performed all operations, and all patients underwent multidisciplinary consultations with surgeons, radiologists, sonographers, anesthesiologists, nutritionists, and rehabilitation professionals before the operation.

Inflow and outflow control before segmentectomy and hemihepatectomy was routinely performed by Pringle maneuver, and the majority of resections were also performed with an intermittent Pringle maneuver. IBL was calculated by using the overall intraoperative volume collected with suction after the subtraction of the lavage volume and the gauze volume, which were weighed to calculate the bleeding volume.

Table 1 Clinicopathologic variables

Variables	N [%]
Age (years)*	
≥60	91 [47]
<60	101 [53]
Gender	
Female	48 [25]
Male	144 [75]
Child-Pugh	
Class A	169 [88]
Class B	21 [12]
Cirrhosis	
Yes	76 [40]
No	114 [60]
HBV infection	
Yes	109 [57]
No	82 [43]
No. of tumors	
Multiple	34 [18]
Solitary	157 [82]
Tumors size (cm)	
≤3	100 [52]
>3	91 [48]
Vascular invasion	
Present	7 [4]
Absent	155 [96]
Diabetes mellitus	
Yes	18 [9]
No	174 [91]
Operative time (min)	
≥166	72 [38]
<166	120 [62]
IBL (mL)	
≤250	97 [51]
>250, <500	95 [49]
≥500, <1,000	60 [31]
≥1,000	25 [13]

Table 1 (continued)

Table 1 (continued)

Variables	N [%]
Blood transfusion	
Yes	40 [22]
No	142 [78]

*, median age: 58 (range: 20–86) years. HBV, hepatitis B virus; IBL, intraoperative blood loss.

Definition of complications

Postoperative complications were defined and classified according to the modified Clavien-Dindo classification (20).

Statistical analysis

Quantitative variables are expressed as mean ± standard deviation, and qualitative variables are expressed as frequencies (percentages). A Student *t*-test or Mann-Whitney U test was used for intergroup comparisons of quantitative variables when appropriate, whereas a Chi-square test or Fisher's exact test was used to compare categorical data. The OS and RFS were calculated by using the Kaplan-Meier method. The log-rank test compared differences between the groups of patients. All P values were two-sided, and a P value less than 0.05 was considered statistically significant.

Moreover, a Cox proportional hazards model was used for multivariate analysis to identify independent prognostic factors. Only potential predictive factors through a univariate analysis ($P < 0.05$) were taken into the Cox model. The hazard ratio (HR) and 95% confidence interval (CI) were used to estimate the role of each independent prognostic factor. All statistical analyses were performed with SPSS version 23.0 software (IBM Corporation, Armonk, NY, USA).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Ethics Board of Sir Run Run Shaw Hospital of Zhejiang University (No. 20190821-6) and individual consent for this retrospective analysis was waived.

Results

Clinical characteristics of patients

The clinical characteristics of the 192 HCC patients

Table 2 Surgical characteristics and surgical outcomes compared to two groups

Variables	Group A (n=97)	Group B (n=95)	Univariate, P	Multivariate, P
Type of resection			0.001*	
Hemihepatectomy	8	26		
Segmentectomy	63	52		
Wedge resection	26	17		
Total operation time (min)	126.65±59.68	206.28±109	0.000*	
Blood transfusion	3	37	0.000*	
General complications	15	25	0.227	
Pulmonary complication	1	7		
Cardiac arrhythmia	2	2		
Ascites	3	2		
Surgical complications				
Wound infection	1	1		
Intra-abdomen infection	2	7		
Intra-abdomen bleeding	2	1		
Biliary fistula/leakage				
Grade B or above*	4	5		
With complications of Clavien				
Dindo grade IIIA or above	–	–		
Clavien-Dindo grade				
III	3	3		
IV	0	2		
V	0	0		
Hospital mortality	0	0		
Hospital stay, d				
>9	27	57		
≤9	70	38		

*, P<0.05 is statistically significant.

are summarized in *Table 1*. There were 144 males and 48 females, with a median age of 58 (range: 20–86) years. The median IBL was 250 (range: 5–5,000) mL. Fifty-seven percent of the patients carried HBV, while 57% also had cirrhosis, though only 12% of them were ranked class B by a Child-Pugh score. Median preoperative serum levels included 11.88 (range: 1–107,583) ng/mL of alpha-fetoprotein (AFP), 31 (range: 12–515) U/L of aspartate

aminotransferase (AST), 29 (range: 3–449) U/L of alanine aminotransferase (ALT), while total bilirubin was 14.4 (range: 2–107) μmol/L, and albumin was 40.2 (range: 5–54) g/L. Tumor size varied from 1.0 to 12.0 cm (median: 3.0 cm), and only 4% of the patients had a vascular invasion. The vast majority (84%) of patients had a single tumor. The median operative time was 142.5 (range: 40–800) min, and the blood transfusion rate was only 20%. The median OS

was 36 (range: 0–216) months.

Postoperative complications

Complications were assessed following surgery and included specific surgery-related morbidity (bile leak, liver failure, and ascites) and general postoperative complications (respiratory complications, cardiac events, gastrointestinal complications, intra-abdominal infection, and neurologic events). The surgical characteristics and surgical outcomes of the two groups are shown in *Table 2*. The morbidity rate and severe complications of the two groups did not differ significantly.

Risk factors for increased IBL during LH for HCC

Only 20% of the 192 patients analyzed required a blood transfusion despite 32% having IBL greater than 500 mL and 13.5% having IBL greater than 1,000 mL. The median IBL was 250 (range: 5–5,000) mL. In *Table 3*, the pathological features of the patients who had less than 250 mL of IBL are compared to the patients who had more than 250 mL. We determined that tumor size, type of hepatectomy, and operative time had a significant association with a high level of blood loss through our univariate analysis. However, our multivariate analyses showed that only the type of hepatectomy and operative time contributed to a higher level of bleeding.

Using IBL to predict survival after LH

The mean and median OS of patients after LH were 39 and 36 months, respectively, while the mean and median RFS after LH were 24.5 and 24 months. The 3- and 5-year OS rates were 53.1% and 24.5%, respectively, while the 3- and 5-year RFS rates were 38% and 16.7%, respectively (*Figure 1*). To determine which pathological features were associated with OS after LH, we used the Kaplan-Meier analysis method. Some of the more significant risk factors determined through our univariate and multivariate analysis included tumor size >3 cm, number of tumors >1, and IBL >250 mL (*Figure 2*). The odds ratio (OR) of these factors were 2.3 [95% CI: (1.4–3.8), P<0.01], 0.5 [95% CI: (0.3–0.8), P<0.01], and 0.5 [95% CI: (0.3–0.9), P<0.02], respectively (*Table 4*).

Predictors of recurrence after LH

The general median recurrence time was 24 months and

was significantly associated with IBL (*Figure 2*). Tumor size >3 cm, number of tumors >1, and IBL >250 mL were significant predictors of HCC recurrence in our multivariate analysis (*Table 5*). The OR for these factors were 2.2 [95% CI: (1.3–3.7), P<0.01], 0.4 [95% CI: (0.23–0.8), P<0.02], and 0.5 [95% CI: (0.3–0.8), P<0.02], respectively.

The degree of IBL decreases OS and RFS

Patients were divided into two groups according to the degree of blood loss (Group A: ≤250 mL; Group B: >250 mL). We noted that the median RFS and OS decreased significantly with the increase of blood loss (*Figure 3*).

The degree of IBL decreases RFS after LH

A Kaplan-Meier analysis was performed to determine which clinicopathologic factors were associated with RFS after LH. Through univariate analysis, we found that tumor size and IBL (*Figure 3*) were significant predictors (*Table 6*), while our multivariate analysis determined that IBL was the only significant predictor of HCC recurrence (*Table 6*, P<0.05).

Discussion

This is the first article that confirms that IBL is an independent predictor of HCC patients who underwent LH long-term survival. Our data shows that the degree of IBL is related to a patient's OS and RFS after LH. In addition, tumor size and the number of tumors can also predict survival in HCC patients who underwent LH. However, advances in surgical techniques and anesthesia have made LH safer (21) and in some cases even better than OH (22–24), the amount of IBL related to LH is still a significant concern. Several clinicopathologic factors such as transfusion (25,26), surgery approach (27,28), and hepatic inflow occlusion (29) are of prognostic importance in patients with HCC after LH. Compared to OH, only a few articles have reported how blood loss affects patients' short-term outcomes during LH (8). However, Tranchart has recommended that 10–14 mmHg pneumoperitoneum, low central venous pressure (<5 cmH₂O), laparoscopy facilitated inflow and outflow control, and experienced laparoscopy surgical skills can effectively control bleeding (30). IBL has been noted as an independent prognostic factor for tumor recurrence and death (9), as well as for a worse survival rate for patients undergoing LH for colorectal cancer

Table 3 Predictors of IBL in LH

Variables	≤250 mL (n=97)	>250 mL (n=95)	Univariate, P	Multivariate, P
Age (years)			0.183	
≥60	40	51		
<60	57	44		
Gender			0.454	
Male	75	69		
Female	22	26		
HBV infection			0.414	
Yes	77	32		
No	54	28		
Liver cirrhosis			0.051	
Yes	26	40		
No	32	37		
Tumor size (cm)			0.025*	0.068
>3	19	18		
≤3	112	42		
No. of tumors			0.731	
Multiple	18	16		
Solitary	78	79		
Vascular invasion			0.664	
Yes	3	4		
No	80	76		
Type of hepatectomy			0.001*	0.001*
Wedge	26	17		
Segmentectomy	63	52		
Hemihepatectomy	8	26		
Operative time (min)				
≥166	23	49		
<166	74	46		

*, P<0.05 is statistically significant. IBL, intraoperative blood loss; LH, laparoscopic hepatectomy; HBV, hepatitis B virus.

liver metastases (18). In our study, only a small number of patients had advanced cirrhosis (12%), which may be the reason why cirrhosis was not a significant predictor of blood loss. LH's effect on patients with HCC and Child-Pugh class B liver disease should be further evaluated in future studies. Through our multivariate analysis, we determined that tumor size, operative time, and the type of hepatectomy

were associated with blood loss (*Table 3*). The relationship between tumor size and bleeding has been reported previously. In 22% of the study's 192 patients, the tumor was larger than 5 cm in diameter and required a longer operative time, resulting in higher blood loss (31). The type of hepatectomy (hemihepatectomy) was also closely related to blood loss and operative time, with a prolonged operative

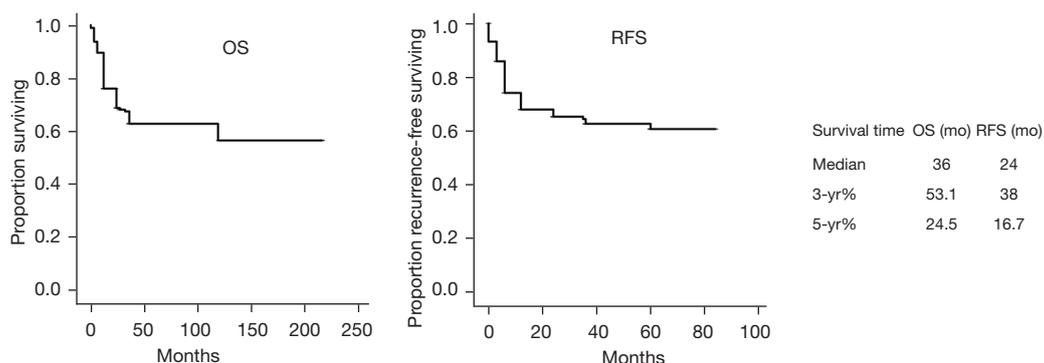


Figure 1 Kaplan-Meier estimates of survival and recurrence for the entire group of patients (n=192). OS, overall survival; RFS, recurrence-free survival.

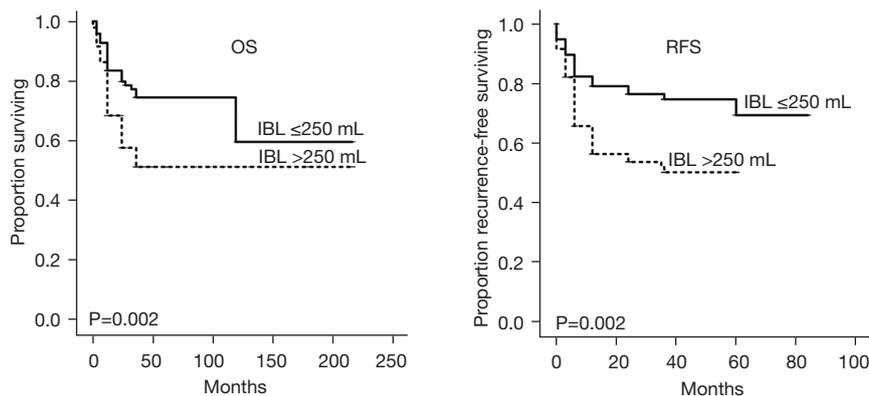


Figure 2 Kaplan-Meier estimates of OS and RFS for patients by IBL. OS, overall survival; RFS, recurrence-free survival; IBL, intraoperative blood loss.

time meaning an increase in blood loss. Thus, operative time and type of hepatectomy were dependent risk factors for increased IBL. This makes it easier to understand that the more complicated the resection, the longer the operative time. Therefore, the impact of hemihepatectomy on the long-term outcome of patients was significantly lower than other factors (Figure 3).

Through the univariate analysis, IBL and tumor size were the independent predictors of RFS in LH (Table 6, Figure 4), whereas multivariate analysis found IBL was the only independent predictor of RFS (Table 6). Our data demonstrated that LH was a predictor of a higher IBL and worse oncologic outcome. At the same time, we also observed that several patients with HCC recurrence undergoing secondary surgery, transcatheter arterial chemoembolization, oral chemotherapy, microwave radiofrequency ablation, and other methods had a

significantly prolonged survival time. This also explains why the degree of blood loss affected the RFS time more significantly than the OS time of the patients.

The degree of IBL was also found to predict the OS and RFS. Patients were divided into two groups according to the degree of blood loss (Group A: ≤ 250 mL; Group B: >250 mL), with the median RFS and OS decreasing significantly with an increased IBL. This further clarified the significant effect bleeding has on the OS and RFS time. In a high-quality publication by Katz (9), he found that IBL independently predicted OS and RFS after LH. He pointed out that more blood loss results in a longer operative time, organ hypoperfusion, and oxygen deficiency. Researchers on other types of cancer (32) have also illustrated the independent effect of bleeding on HCC recurrence, with the leading cause being anti-tumor immunosuppression.

Many reports have also suggested that a blood transfusion

Table 4 Predictors of OS in LH

Variables	Median (MO)	P	Multivariate, OR (95% CI), P
Age (years)		0.213	
≥60	32		
<60	36		
Gender		0.182	
Male	36		
Female	35		
Liver cirrhosis		0.051	
Yes	36		
No	36		
HBV infection		0.508	
Yes	36		
No	34		
Tumor size (cm)		0.000*	2.3 (1.4–3.8), <0.01*
>3	24		
≤3	37		
No. of tumors		0.016*	0.5 (0.3–0.8), <0.01*
Multiple	23.5		
Solitary	36		
Vascular invasion		0.426	
Yes	12		
No	36		
Type of hepatectomy		0.263	
Wedge	36		
Segmentectomy	36		
Hemihepatectomy	24		
Operative time (min)		0.382	
≥166	36		
<166	36		
Blood transfusion		0.139	
Yes	31		
No	36		
IBL (mL)		0.002*	0.5 (0.3–0.9), <0.02*
>250	24		
≤250	36		

*, P<0.05 is statistically significant. OS, overall survival; LH, laparoscopic hepatectomy; MO, month; OR, odds ratio; CI, confidence interval; HBV, hepatitis B virus; IBL, intraoperative blood loss.

Table 5 Predictors of RFS in LH

Variables	Median (MO)	P	Multivariate, OR (95% CI), P
Age (years)		0.269	
≥60	14		
<60	24		
Gender		0.168	
Male	24		
Female	18		
Liver cirrhosis		0.032*	0.099
Yes	24		
No	24		
HBV infection		0.697	
Yes	24		
No	14.5		
Tumor size (cm)		<0.01*	2.2 (1.3–3.7), <0.01*
>3	12		
≤3	24		
No. of tumors		0.017*	0.4 (0.3–0.8), <0.01*
Multiple	9		
Solitary	24		
Vascular invasion		0.349	
Yes	6		
No	24		
Type of hepatectomy		0.2	
Wedge	24		
Segmentectomy	24		
Hemihepatectomy	12		
Operative time (min)		0.385	
≥166	24		
<166	24		
Blood transfusion		0.099	
Yes	12		
No	24		
IBL (mL)		<0.01*	0.5 (0.3–0.8), <0.02*
>250	9		
≤250	24		

*, P<0.05 is statistically significant. RFS, recurrence-free survival; LH, laparoscopic hepatectomy; MO, month; OR, odds ratio; CI, confidence interval; HBV, hepatitis B virus; IBL, intraoperative blood loss.

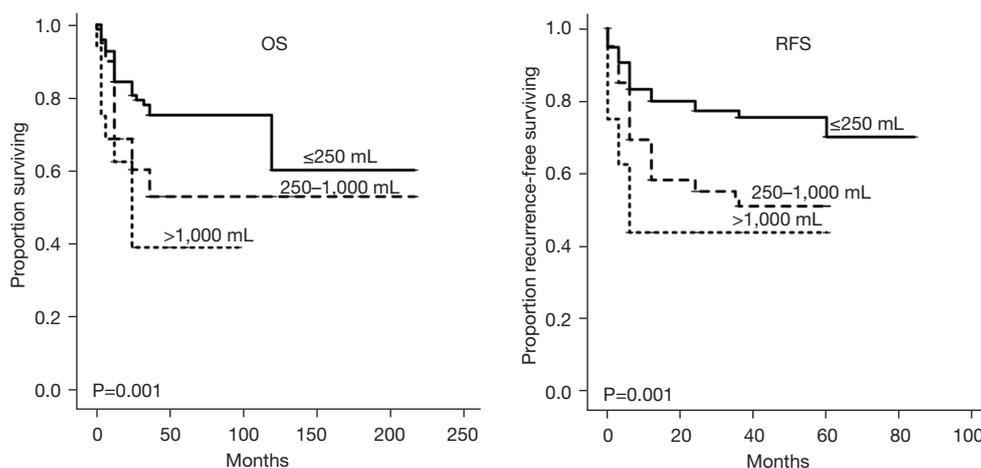


Figure 3 Dose-response relationships of IBL and OS, RFS. IBL, intraoperative blood loss; OS, overall survival; RFS, recurrence-free survival.

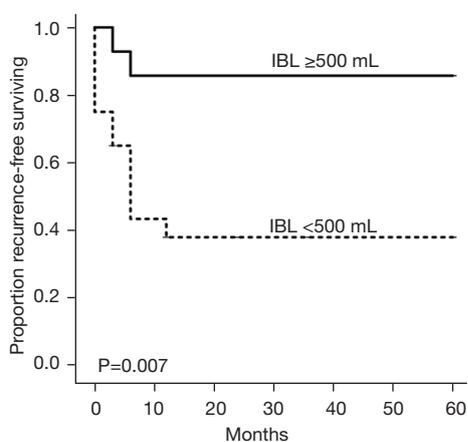


Figure 4 Kaplan-Meier estimates of RFS for laparoscopic major hepatectomy. RFS, recurrence-free survival; IBL, intraoperative blood loss.

while undergoing OH is a significant predictor of patient outcomes (12,27,28,33). However, in our study, transfusion did not obtain a statistical significance for OS and RFS. The low transfusion rate (22%) in our study may account for this. Compared to OH, LH results in less blood loss and can therefore reduce the need for blood transfusions.

Regarding the short-term outcomes of the patients analyzed, there were no significant differences determined. Only 41 of the 192 patients had complications after LH. Several studies (22-24) have also proved that LH is better than OH in terms of short-term outcomes, and these findings are consistent with our results. The type

of hepatectomy is also an important factor that influences the degree of bleeding. In our study, wedge and segmental resection were implemented in 65% of the cases, while hemihepatectomy was only used for 35%. This may explain why there were fewer postoperative complications and why the complication rate was low in our study. In our next study, we will continue to explore the relationship between LH and the short- and long-term outcomes of HCC patients.

Our report also confirms that in experienced hands, LH is safe and effective, leading to less blood loss and shorter hospital stays. Diversified methods improve the survival time of HCC patients after LH and improve their quality of life.

It is also important to note that our study had certain limitations. These included the follow-up time not being long enough and for which, in future studies, we will strive to increase to a period of more than 10 years. The sample size of the study could have also been expanded. However, as the center involved in the study specializes in LH, there will be more and more cases to study in the future and more advanced technologies involved. Overall, this will result in less bleeding, shorter hospital stays, and higher survival rates for HCC patients undergoing LH.

Conclusions

To conclude, we found that the degree of IBL is an independent predictor of the OS and RFS of HCC patients after LH. Therefore, it is paramount that various methods and surgical instruments be used to reduce IBL during LH.

Table 6 Predictors of RFS in LH

Variables	Median (MO)	P	Multivariate, OR (95% CI), P
Age		0.474	
≥60	12		
<60	24		
Gender		0.737	
Male	12		
Female	12		
Liver cirrhosis		0.685	
Yes	6		
No	12		
HBV infection		0.729	
Yes	12		
No	18		
Tumor size (cm)		0.026*	1.8 (0.6–5.3), 0.32
>3	6		
≤3	24		
No. of tumors		0.11	
Multiple	4.5		
Solitary	18		
Vascular invasion		0.47	
Yes	24		
No	12		
Operative time (min)		0.98	
≥166	12		
<166	18		
Blood transfusion		0.069	
Yes	24		
No	12		
Complications		0.976	
Yes	6		
No	12		
IBL (mL)		0.007*	0.18 (0.04–0.8), 0.024*
>500	12		
≤500	15		

*, P<0.05 is statistically significant. RFS, recurrence-free survival; LH, laparoscopic hepatectomy; MO, month; OR, odds ratio; CI, confidence interval; HBV, hepatitis B virus; IBL, intraoperative blood loss.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Ethics Board of Sir Run Run Shaw Hospital of Zhejiang University (No. 20190821-6) and individual consent for this retrospective analysis was waived.

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