Factors Predicting Survival in Ruptured Hepatocellular Carcinoma Treated with Surgical Resection

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ABSTRACT

Objective: Today, ruptured hepatocellular carcinoma (HCC) is a less frequently encountered problem globally due to availability of cancer surveillance protocols for the high-risk population. However, in Thailand, a number of patients do not enroll in screening programs, leading to high rates of ruptured complications. In fit-for-surgery and clinically stable patients, hepatectomy means long-term survival. This study aimed to identify predictive factors of survival in resected patients.

Materials and Methods: A retrospective review of patients with ruptured HCC who underwent liver resection between January 2013 and December 2019 at Siriraj Hospital was performed. The clinical data and outcomes of patients was analyzed.

Results: A total of forty-two patients with ruptured HCC underwent resection or 9.8% of all operable HCC cases. There were 6 patients (14.3%) who suffered from postoperative liver failure and one patient (2.4%) died within 30 days. Overall survival (OS) and recurrence-free survival (RFS) were 90%, 64%, 52% and 42.5%, 24%, 16% at 1, 3, and 5 years, respectively. The factors affecting OS were tumor size ≥10 cm, vascular invasion, and positive resection margin.

Conclusion: Surgical resection in ruptured HCC provides long-term survival. Predicting factors affecting overall survival were large tumor size, vascular invasion, and positive resection margin. Patient selection is a key for better patient's outcomes.

Keywords: Ruptured hepatocellular carcinoma; surgical resection; risk factors; survival (Siriraj Med J 2022; 74: 40-47)

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common malignancy of the liver and the sixth most common worldwide.[1] In Thailand, HCC is the most common malignancy in males and second-most malignancy in females.[1] Although most HCC patients are asymptomatic, some patients suffer with intra-abdominal bleeding due to a ruptured tumor. The incidence rate of ruptured HCC varies among countries, however, it is more common in Asia than in the West where the rate fluctuates between 3% to 26%.[2] In Thailand, the incidence rate is approximately 12.4%.[3] The outcomes of patients with ruptured HCC

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varies widely depending on the treatment and other factors such as performance status, vital signs on arrival, amount of intraperitoneal hemorrhage, comorbidities and background liver parenchyma disease. Moreover, outcomes of liver resection are significantly better than other treatments with a mortality rate of 4.4% compared to 85-100%, respectively.[4,5] In some reports, patients with ruptured HCC who had surgical resection had similar overall survival (OS) compared to non-ruptured HCC patients.[6-9]

In this study, our aim was to identify predictive factors that affect survival rate in ruptured HCC patients undergoing surgical resection.

MATERIALS AND METHODS

This retrospective study was performed in patients diagnosed with ruptured HCC who had liver resection at Siriraj Hospital between January 2013 and December 2019. The patients were diagnosed with ruptured HCC through preoperative imaging such as ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI), or by the intraoperative finding of hemoperitoneum. The decision to perform a surgery depended on the patient's condition and the attending surgeon. While major hepatectomy was defined as resection of 3 Couinaud's segments or more, minor hepatectomy was defined as resection of less than 3 Couinaud's segments. After a successful liver resection, patients had to follow-up with postoperative imaging using either CT or MRI every 3-6 months to evaluate the surgical outcome and to detect the recurrence of HCC. The definition of HCC recurrence is the appearance of hypervascular patterns in a CT or MRI scan with early enhancement in the arterial phase and rapid washout during the porto-venous phase. The patients who were diagnosed with recurrence were evaluated for the possibility of curative treatments such as resection or ablation. Trans-arterial chemoembolization (TACE), trans-arterial radioembolization (TARE) or other systemic therapies were offered if definitive treatments were not possible.

The outcomes we focused on in this study included overall survival (OS) and disease-free survival (DFS). While OS was defined as the length of time from date of operation to the date of death or last follow-up DFS was defined as the time from the date of operation to the date of confirmed HCC recurrence. An extrahepatic recurrence or peritoneal seeding tumor was confirmed by imaging or pathological reports.

The characteristics of patients with ruptured HCC were analyzed to determine related factors influencing outcomes. This study was approved by the human research committee of Faculty of Medicine Siriraj Hospital, Mahidol University.

Variable data was expressed as mean ± standard deviation (SD) and number (percentage). The OS and DFS values were calculated using the Kaplan-Meier survival analysis. Meanwhile, the univariable and forward stepwise multivariable Cox regression analysis were performed to investigate predictors and all the data was analyzed using SPSS software, version 17.0 [IBM, Illinois].

RESULTS

Between January 2013 and December 2019, a total of 460 patients with HCC underwent surgical resection at Siriraj Hospital. Of the total, 45 patients (9.8%) were categorized as those presenting clinical signs of HCC. However, three patients were excluded from the study due to the incomplete recording of data. Therefore, a total of 42 patients were included in this analysis. Most of patients were males (78.6%) and the average age of patients was 59.5. Fourteen patients (33.3%) showed signs of hypovolemic shock and of this total, 10 (71.4%) required emergency trans-arterial embolization (TAE). Regardless, 6 patients from the non-hypovolemic shock group also underwent TAE due to ongoing bleeding. The average tumor size was 7.9 cm and remarkably, almost all the patients had liver function status defined as Child-Pugh class A (97.6%). The patient demographic data is described in Table 1. Major liver resections were performed in 11 patients (26.2%) and median intraoperative blood loss was 600 mL (range 80 - 5,000 mL). Twenty-six patients (61.9%) had vascular invasion; 7 patients (16.7%) had a positive resection margin. The intraoperative and pathologic outcomes are described in Table 2.

Regarding the postoperative period, one patient (2.4%) died within 30 days due to post-hepatectomy liver failure. The postoperative morbidity rate was 28.6% (12/42) and the median length of stay 6 days (range 4 - 58 days). The median overall survival (OS) was 61.1 months and median follow-up time 22 months. The overall survival was 90%, 64%, 52% at 1, 3, and 5 years respectively (Fig 1A). Meanwhile, recurrence-free survival (RFS) was 42.5%, 24%, 16% at 1, 3, and 5 years respectively (Fig 1B). Twenty-nine patients (69%) had a recurrence of HCC at the median time of 7.5 months. The type of recurrence was intrahepatic recurrence (17/29, 58.6%), intrahepatic and extrahepatic recurrence (10/29, 34.5%), and extrahepatic recurrence (2/42, 6.9%). Seven patients (16.7%) suffered from peritoneal recurrence.

Risk factors that affected OS and RFS were analyzed with a univariable and multivariable Cox regression analysis. At least eight factors (univariable Cox regression analysis) affected OS: the preoperative factors were - tumor size ≥10 cm, macrovascular invasion, hematocrit <30%, time-to-surgery ≤7 days, intraoperative factors - blood

TABLE 1. Demographic data.

Characteristics	n = 42
Patient's characteristics	59.5 ± 13.1
Age (years)	
Gender	
Male	33 (78.6%)
Female	9 (21.4%)
Tumor size (cm)	7.9 ± 3.2
Macrovascular invasion	4 (9.5%)
No. of tumor	
1	37 (88.1%)
2	3 (7.1%)
3	2 (4.8%)
Hypovolemic shock	14 (33.3%)
Preoperative embolization	16 (38.1%)
MELD score	8 (6-14)
Child-Pugh	
grade A	41 (97.6%)
grade B	1 (2.4%)
Time to surgery	
≤7 days	12 (28.6%)
>7 days	30 (71.4%)
Preoperative Laboratory results:	
Total bilirubin (mg/dL)	0.70 ± 0.37
Albumin (mg/dL)	3.88 ± 0.50
Prothrombin time	12.9 ± 1.0
Creatinine	0.93 ± 0.20
Hematocrit (%)	35.6 ± 7.1
AFP	6,522 ± 20,855

Data was presented as mean ± SD, median (range) or number (percentage)

TABLE 2. Intraoperative and pathologic result.

Outcomes	n = 42
Intra-operative outcome	
Type of hepatectomy	
Major	11 (26.2%)
Minor	31 (73.8%)
Operative time (min)	150 (75 – 660)
Intra-operative blood loss (mL)	600 (80 – 5000)
PRC transfusion	18 (42.9%)
Pathological results	
Differentiation	
Moderately	33 (78.6%)
Poor	4 (9.5%)
Extensive necrosis (after embolization)	5 (11.9%)
Vascular invasion	26 (61.9%)
Satellite lesion	9 (21.4%)
Positive margin	7 (16.7%)

Major hepatectomy = liver resection ≥3 Couinaud's segments
Data was presented as mean ± SD, median (range) or number (percentage)

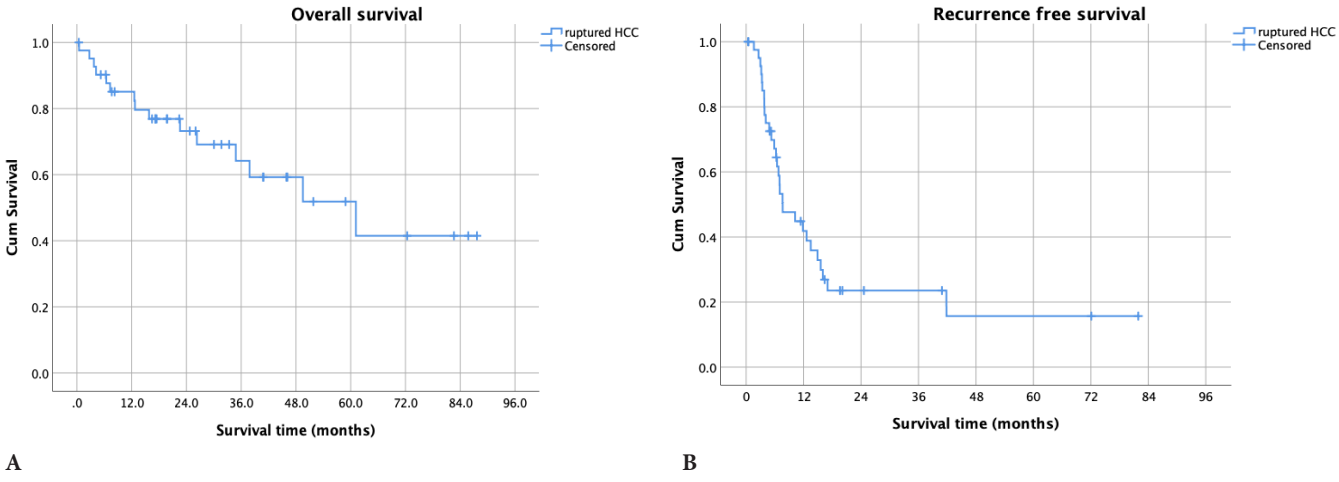

Fig 1. **A**- Kaplan-Meier estimation of overall survival of all patients. 5-year OS was 52%.;
B- Kaplan-Meier estimation of recurrence-free survival of all patients. 5-year DFS was 16%.

loss > 1,000 mL, blood transfusion, and pathological factors - vascular invasion, positive resection margin (Table 3). Using a multivariable analysis, only three factors i.e. tumor size ≥10 cm, vascular invasion, and positive resection margin were documented for OS. There were 3 pathological factors affecting RFS; i.e. vascular invasion, positive resection margin, and satellite lesion (Table 4). Among these factors, tumor size ≥10 cm, time-to-surgery ≤7 days, vascular invasion, positive resection margin were found to be major factors leading to worst OS outcome (Fig 2).

DISCUSSION

Spontaneous rupturing of HCC is a catastrophic complication with a high mortality rate. Today, patients with HCC receive treatment early due to worldwide implementation of surveillance programs in high-risk patients, resulting in less people presenting ruptured HCC. However, the incidence rate of ruptured HCC in Asian countries is higher than in Western countries. In our institution, Siriraj Hospital, the ruptured HCC rate was 9.8% of all resectable HCC cases, which is comparable to reports from other Asian countries such as Hong Kong (9%)[10], Taiwan (26%)[11], and Japan (2.3%).[12]

Ruptured HCC usually shows aggressive tumor biology. According to our data, there was high rate of vascular invasion (61.9%) and 9 patients (21.4%) had a large tumor of over 10 cm. In this study, patients with tumor size ≥10 cm, vascular invasion, and positive tumor margin had significant shorter overall survival rate.

This study provided results of long-term survival with low morbidity in select surgical candidates. However, almost all operable cases had a well-preserved liver function (CTP-A, 97.6%) and most operations were partial hepatectomies (73.8%). The strategy of using non-urgent surgical resections despite tumor bleeding was stopped, either spontaneously or by embolization. The surgery was performed after patient condition was stabilized. Surgery performed within 7 days significantly affected the overall survival. Moreover, post-hepatectomy liver failure was encountered only in 6 patients (14.3%) with only one case of mortality (2.4%). The 5-year overall survival was 52%, which is better than results in several other studies[4,6,7] and comparable with some large series.[8,13] This study strongly demonstrates that surgical resection plays a role in the treatment of ruptured HCC patients including those at the advanced tumor stage.

Peritoneal recurrence is uncommon in non-ruptured HCC when compared to the high rates of ruptured HCC. Peritoneal recurrence was found only in 16.7% of patients in this study and this was comparable to previous studies which reported a rate between 11 - 40% with median time to recurrence being 6 - 11 months.[14-18] Ruptured HCC and time-to-surgery were the two most common deciding factors for peritoneal recurrence, however, there is some supportive and contradictive evidence regarding this.[14,15,19,20]

Most ruptured HCC patients usually presented poor liver function and were excluded from liver resection. Therefore, the number of ruptured HCC patients who could be candidates for liver resection was limited. Nevertheless, a further prospective study with a large number of ruptured HCC patients, including a multicenter study should be carried out to clarify additional predictive factors of ruptured HCC patients treated with surgical resection.

TABLE 3. factors affecting overall survival of ruptured HCC undergoing resection by univariable and multivariable Cox regression analysis.

Factors	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Pre-operative factors						
Age: ≥60 years	0.664	0.235 – 1.879	0.44			
Pre-operative hypotension	0.658	0.196 – 2.208	0.50			
Pre-operative embolization	0.675	0.230 – 1.979	0.47			
Tumor size ≥10 cm	**3.987**	**1.234 – 12.88**	**0.02**	**5.487**	**1.387 – 21.72**	**0.02**
Macrovascular invasion	**5.621**	**1.442 – 21.92**	**0.01**			
Multiple tumor	1.856	0.514 – 6.700	0.35			
MELD score >8	1.892	0.662 – 5.406	0.23			
Time-to-surgery: ≤7 days	**4.063**	**1.398 – 11.81**	**0.01**			
Laboratory results:						
Total bilirubin >1.0 mg/dL	1.648	0.548 – 4.960	0.37			
Albumin <3.5 mg/dL	1.800	0.568 – 5.708	0.32			
Hematocrit <30 %	**4.011**	**1.193 – 13.481**	**0.03**			
Prothrombin time >13 second	1.237	0.438 – 3.494	0.67			
AFP >200 IU/mL	1.930	0.644 – 5.778	0.24			
Intra-operative factors						
Major hepatectomy	2.272	0.656 – 7.871	0.20			
Operative time: ≥180 min	1.436	0.464 – 4.450	0.53			
Blood loss >1000 mL	**3.803**	**1.347 – 10.74**	**0.01**			
Blood transfusion	**4.013**	**1.355 – 11.89**	**0.01**			
Pathological factors						
Vascular invasion	**7.068**	**1.581 – 31.60**	**0.01**	**6.165**	**1.195 – 31.80**	**0.03**
Positive resection margin	**4.881**	**1.204 – 19.79**	**0.03**	**9.663**	**1.181 – 79.06**	**0.03**
Satellite lesion	1.297	0.356 – 4.724	0.69			

TABLE 4. factors affecting recurrence of ruptured HCC undergoing resection by univariable and multivariable Cox regression analysis.

Factors	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Pre-operative factors						
Age: ≥60 years	0.746	0.357 – 1.558	0.44			
Pre-operative hypotension	0.543	0.218 – 1.349	0.19			
Pre-operative embolization	0.697	0.327 – 1.487	0.35			
Tumor size ≥10 cm	0.927	0.370 – 2.320	0.87			
Macrovascular invasion	1.125	0.337 – 3.759	0.85			
Multiple tumor	1.989	0.672 – 5.884	0.21			
MELD score >8	1.877	0.825 – 4.273	0.13			
Time-to-surgery: ≤7 days	1.642	0.755 – 3.571	0.21			
Laboratory results:						
Total bilirubin >1.0 mg/dL	1.103	0.441 – 2.756	0.83			
Albumin <3.5 mg/dL	1.064	0.397 – 2.851	0.90			
Hematocrit <30 %	1.430	0.541 – 3.784	0.47			
Prothrombin time >13 second	1.061	0.484 – 2.324	0.88			
AFP >200 IU/mL	1.151	0.500 – 2.652	0.74			
Intra-operative factors						
Major hepatectomy	0.876	0.354 – 2.163	0.77			
Operative time: ≥180 min	0.653	0.275 – 1.551	0.33			
Blood loss >1000 mL	0.644	0.271 – 1.532	0.32			
Blood transfusion	0.773	0.361 – 1.653	0.51			
Pathological factors						
Vascular invasion	**2.295**	**1.044 – 5.049**	**0.04**	**2.590**	**1.153 – 5.819**	**0.02**
Positive resection margin	**5.174**	**1.838 – 14.56**	**<0.01**	**5.753**	**1.835 – 18.04**	**<0.01**
Satellite lesion	**3.051**	**1.317 – 7.070**	**<0.01**	**3.052**	**1.273 – 7.318**	**0.01**

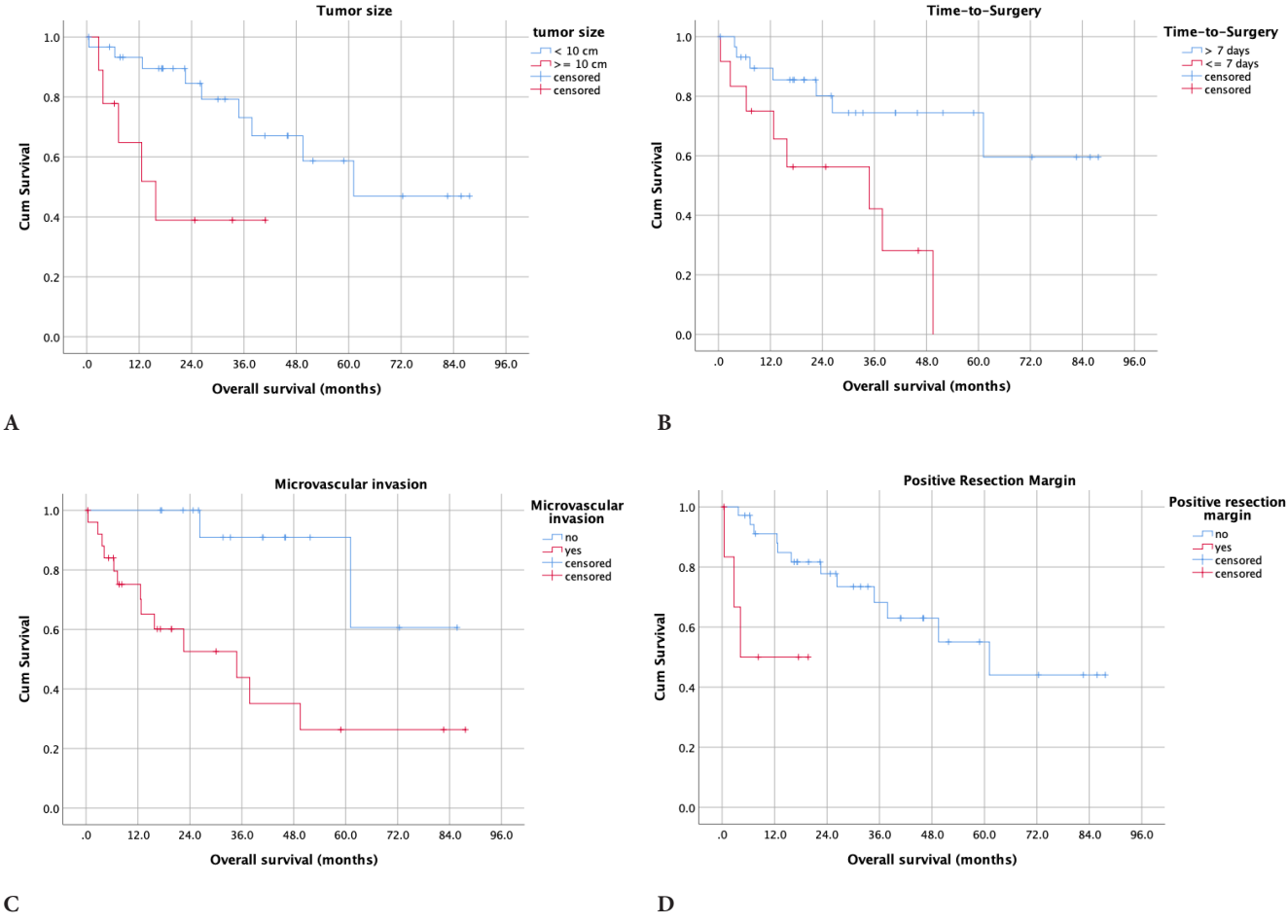

Fig 2. Kaplan-Meier estimation of overall survival of patients. **A:** Patients with Tumor size ≥ 10 cm had significantly poor OS (median OS 61.1 months [size <10 cm] vs 15.8 months [size ≥10 cm], p = 0.01); **B:** Time-to-Surgery ≤7 days had significantly poor OS (median OS 34.8 months [≤7 days] vs Not reach [>7 days], p <0.01); **C:** HCC with microvascular invasion had significantly poor OS (median OS 34.8 months [with vascular invasion] vs not reach [without vascular invasion], p <0.01); **D:** Patients with positive resection margin had significantly poor OS (median OS 61.1 months [free resection margin] vs 4.2 months [positive resection margin], p = 0.01)

CONCLUSIONS

Surgical resection in ruptured HCC provides long-term survival. Predicting factors affecting overall survival were large tumor size, vascular invasion, and positive resection margin. Patient selection is a key for better patient's outcomes.

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