Original Article

Predictive Factors of Mortality in Ruptured Hepatocellular Carcinoma

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Background: Ruptured hepatocellular carcinoma (HCC) globally carries a high mortality rate. In Thailand, the incidence of ruptured HCC remains high and the data is still lacking. This study aims to identify the predictive factors of death in these patients.

Materials and methods: This study is a retrospective review of 4,330 patients diagnosed with HCC admitted at Siriraj Hospital from January 2012 to June 2018. Forty-five patients diagnosed with ruptured HCC were included in this study. The patients were divided into a survivor group and a mortality group. Demographic data, clinical manifestations, biochemical data, tumor characteristics, and therapeutic procedures were collected. The mortality rate and factors associated with mortality were analyzed.

Results: 10 patients and 35 patients were categorized in the survivor group and the mortality group, respectively. Demographic data between the two groups were comparable. Emergency hemostasis was achieved with transarterial embolization (TAE) in 40% of survivor group and 65% of mortality group. In survivor group, hepatectomy could be achieved in 80% of the patients. The multivariate analyses found that the predictive factors of death in ruptured HCC were the inability to undergo further definitive hepatectomy ($p = 0.04$) and high serum creatinine level ($p = 0.01$). Overall survival of ruptured HCC patients at 1-month, 1-year, and 3-year were 76.0%, 26.4%, 13.2%, respectively. Overall survival after hepatectomy at 1-month, 1-year, and 3-year were 100%, 100% and 75%, respectively.

Conclusion: The predictive factors of death in ruptured HCC patients were the inability to undergo further hepatectomy and high serum creatinine level. Patients who underwent hepatectomy as a definitive treatment could achieve a better survival outcome after ruptured HCC.

Keywords: Ruptured, Hepatocellular carcinoma, Transarterial embolization, Hepatectomy, Survival

J Med Assoc Thai 2020;103(Suppl.5): 75-81
Website: http://www.jmatonline.com

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, associated with 80% of patients with cirrhosis[1,2]. The major causes of cirrhosis are hepatitis B, hepatitis C, and alcohol. Although the incidence of HCC is accounting for 1/6th of all carcinomas, it is the third leading cause of cancer-related deaths worldwide[3]. One of the most common causes of death from patients with HCC was ruptured hepatocellular carcinoma.

Ruptured hepatocellular carcinoma is one of the life-threatening presentations of this disease. The reported incidence was 3 to 15% in cirrhotic patients[4]. Interestingly, the incidence of ruptured HCC may be declining due to earlier detection of HCC and therefore earlier stage of presentation. Presentation ranges from non-specific symptoms, such as sudden abdominal pain for 66 to 100%, or shock in 33 to 90% of patients. Unfortunately, no clinical applications have been developed, and consequently, 30-day mortality rates, despite recent improvements in management, still range between 25 and 75%[4-8]. These high rates of mortality are due to the critical conditions of patients at admission, related to liver function at the time of rupture and the severity of bleeding. Initial management is decided upon based on these parameters, and a well-accepted treatment of choice is a non-surgical approach, particularly transcatheter arterial embolization (TAE).

Although the incidence remains high in Asian countries, there is still a lack of significant data, especially in Thailand. The aim of the present study was to identify the predictive factors of mortality in ruptured HCC.

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Materials and Methods

Population selection

Data from patients diagnosed with ruptured HCC, admitted to the surgical unit, during the period from January 2012 to June 2018 were retrospectively retrieved from the databases of the Department of Surgery, Faculty of Medicine Siriraj hospital, Mahidol University.

The current study was performed with the

How to cite this article: Mahawithitwong P, Charoensilavath D, Sirivatanauksorn Y, Limsrichamrern S, Kositamongkol P, Tovikkai C, Dumronggittigule W, Sangserestid P. Predictive Factors of Mortality in Ruptured Hepatocellular Carcinoma. J Med Assoc Thai 2020;103(Suppl.5): 75-81.

approval of the Siriraj Institutional Review Board (142/2561(EC4)). The specific written informed consent of patients was not required for this observational study.

Review of clinical, laboratory data, and imaging

Clinical data collected for all of the patients included age, BMI, sex, previous history of liver cirrhosis treatment, cause of cirrhosis, Child-Turcotte-Pugh (CTP) score, presence of abdominal pain or distention, blood on abdominal tapping, shock, administration of blood transfusions, number of hospitalization days and outcome.

Initial relevant laboratory data were also evaluated. Imaging features, including tumor multiplicity, laterality, size, and location were recorded.

Treatment options

The treatment options could be divided into two phases. Firstly, the emergency treatment in order to stop the bleeding with transarterial embolization (TAE) or conservative treatment. TAE was considered as the first line of treatment in patients with reasonable liver function without complete portal vein thrombosis. Conservative treatments such as correction of coagulopathy, continuing resuscitation and close monitoring were decided for patients with the moribund state or for stable patients without signs of continuous bleeding. The second phase is definite treatment that could be divided into four groups including hepatectomy, transarterial chemoembolization, other modalities (such as radiofrequency ablation, transarterial radioembolization, sorafenib), and supportive treatment. Decision-making was performed using a multidisciplinary team, which included hepatopancreatobiliary (HPB) surgeons, intervention radiologists, and oncologists.

Follow-up

In-hospital complications were closely monitored and classified with Clavien-Dindo classification. Liver failure rates were also recorded to find out the predictive factors of death. After discharge from hospital or emergency treatment, patients were followed-up for re-evaluation of definite treatment. The follow-up course would continue until the end of the disease.

Statistical analysis

Patients could be divided into 2 groups: the survivor group and the mortality group. The primary objective of the study is to identify the predictive factors of mortality in ruptured HCC. The secondary objectives are providing treatment outcome and survival rate.

The patients' characteristics were analyzed to determine whether the prognostic factors influenced mortality. Continuous variables were expressed with Unpaired t-test or Mann-Whitney U-test, and categorical variables were expressed as a number using Chi-square of Fischer's exact test. The survival rate was analyzed using Kaplan-Meier method with the log-rank test. The factors that were significant in univariate analysis were calculated with multivariate Cox analysis. The *p*-value less than 0.05 was considered statistically significant. All statistical analyses were performed with PAWS statistics version 18.0 for PC.

Results

Clinical characteristics of patients

Forty-five patients were enrolled in this study. The data were allocated to two groups as a survivor group (n = 10) and a mortality group (n = 35). Demographic data, cause of cirrhosis, clinical presentation, initial laboratory exam, liver function test, and tumor characteristics were comparable between the two groups (Table 1, 2). The majority of patients with ruptured HCC were of male gender. Most of them were diagnosed with cirrhosis from ruptured HCC. Viral hepatitis is the most common cause of cirrhosis among two groups with 60% and 77%, in survivor and mortality group, respectively. There were no statistically significant differences in clinical presentations between the two groups.

Treatment and outcomes

The emergency treatments for hemostasis control were TAE in 27 patients and conservative treatment in 18 patients. The mortality rate in TAE group was higher than those in the conservative group, 65% (23 patients) and 34% (12 patients), respectively. Interestingly, the survival rate in the conservative group is better than those in the TAE group, 60% (6 patients) compared to 40% (4 patients). Nevertheless, there was no statistical difference in mortality ($p = 0.143$) between both TAE and conservative groups (Table 3). Regarding definite treatment, the patients who underwent hepatectomy had significantly better survival than those who received other treatments, including conservative treatment, TACE alone and other modalities ($p<0.001$).

The complication rate in the survivor group was found only in one patient (10%, Clavien-Dindo class I), while in the mortality group was found in 11 patients (17% Clavien-Dindo class I-II and 14% Clavien-Dindo class III-IV). There was no incidence of liver failure in the survivor group, whereas it was evident in about 14% in the mortality group.

Independent variables associated with mortality

To adjust for potential confounders including all the demographic, clinical characteristics, treatment, and complications, Cox-regression was utilized to analyze prognostic factors for mortality. The results of univariate Cox-regression (crude hazard ratio [HR]) and multivariate model (adjusted HR) adjusted for all other factors were shown in Table 3. Variables significant in univariate regression are high hemoglobin, high level of serum creatinine, high CTP score (B and C), PRC and FFP transfusions, conservative treatment or inability to undergo hepatectomy, higher level of complications (Clavien-Dindo: III and IV), and patients with liver failure. The significant prognostic factors for univariate analysis were adjusted with multivariate analysis. After multivariate analysis was applied, there were two independent predictive factors, including high serum creatinine level (HR = 2.408, 95% CI: 1.027 to 5.645, *p*-value = 0.043)

Table 1. Demographic data of ruptured HCC patients

Variable	Number (%)		*p*-value
	Survivor group (n = 10)	Mortality group (n = 35)	
Gender			0.589
Male	8 (80)	25 (71.4)	
Female	2 (20)	10 (28.6)	
Known history of HCC	0 (0)	9 (25.7)	0.073
Previous treatment of HCC	0 (0)	8 (22.9)	0.095
Cause of Cirrhosis			0.745
Viral-related	6 (60)	27 (77.1)	
Alcoholic	1 (10)	1 (2.9)	
Others*	3 (30)	7 (20)	
Child-Turcotte-Pugh (CTP) score			0.098
A	7 (77.8)	13 (39.4)	
B	1 (11.1)	16 (48.5)	
C	1 (11.1)	4 (12.1)	
Clinical presentation			
Abdominal pain	10 (100)	33 (94.3)	0.439
Abdominal distension	4 (40)	23 (65.7)	0.143
Blood on abdominal tapping	1 (10)	7 (20)	0.466
Shock	5 (50)	12 (34.3)	0.366

* Others included NASH, cryptogenic, miscellaneous

Table 2. Clinical data of ruptured HCC patients, continuous data

Variable	Mean ± SD or median (min-max)		*p*-value
	Survivor group (n = 10)	Mortality group (n = 35)	
Age (year)	47 (34 to 72)	59 (27 to 86)	0.105
BMI (kg/m^2)*	23.75±4.44	22.96±3.45	0.569
Blood chemistries			
Hb (g/dl)	10.6 (8.2 to 11.5)	9.3 (5.4 to 12.0)	0.356
Hct (%)*	30.9±3.53	28.89±5.47	0.302
WBC	11,230 (6,230 to 26,440)	11,200 (8,100 to 59,400)	0.557
Platelet (/ul)	112,000 (81,000 to 594,000)	179,000 (63,000 to 622,000)	0.863
BUN (mg/dl)	17.1 (4.9 to 31.1)	16.8 (7.5 to 98.0)	0.452
Cr (mg/dl)	0.90 (0.59 to 1.45)	1.20 (0.50 to 6.40)	0.355
Alb (g/dl)*	3.2 (2.6 to 4.0)	3.0 (2.1 to 4.4)	0.046
Glb (g/dl)*	3.36±0.60	3.64±0.80	0.319
TB (mg/dl)	1.20 (0.43 to 4.0)	1.30 (0.44 to 33.0)	0.177
DB (mg/dl)	0.49 (0.17 to 2.56)	0.71 (0.16 to 26.94)	0.053
AST (U/L)	88 (33 to 473)	162 (36 to 1,765)	0.540
ALT (U/L)	68 (14 to 341)	55 (21 to 949)	0.842
ALP (U/L)	79 (49 to 157)	132 (38 to 453)	0.132
PT (sec)	12.9 (12.0 to 15.7)	14.5 (10.6 to 70.5)	0.054
INR	1.13 (1.09 to 1.26)	1.19 (1.00 to 27.60)	0.317
Tumor characteristics			
Size (cm)*	7.84±2.00	9.17±4.25	0.370
Number of tumors	1 (1 to 5)	3 (1 to 10)	0.070
Number of ruptured tumors	1 (1 to 1)	1 (1 to 1)	0.599

and the patient's inability to undergo hepatectomy as definite treatment (compared with other treatments) (HR = 15.485, 95% CI: 1.983 to 123.731, $p = 0.01$).

Overall survival

The cumulative overall survival rates of all ruptured HCC patients are 76.2% at 1 month, 20.4% at 1 year, and

Table 3. Treatment and complications

Variable	Number (%)		*p*-value
	Survivor group (n = 10)	Mortality group (n = 35)	
Emergency treatment			0.143
Transarterial embolization (TAE)	4 (40)	23 (65.7)	
Conservative treatment	6 (60)	12 (34.3)	
Definite treatment			< 0.001
Conservative treatment	1 (10)	19 (54.3)	
Hepatectomy	8 (80)	1 (2.9)	
TACE	1 (10)	13 (37.1)	
Other treatment modalities	0 (0)	2 (5.7)	
Complication (Clavien-Dindo classification)			0.896
No	9 (90)	24 (68.6)	
I	1 (10)	3 (8.6)	
II	0 (0)	3 (8.6)	
III	0 (0)	3 (8.6)	
IV	0 (0)	2 (5.7)	
Liver failure			1.000
No	10 (100)	30 (85.7)	
A	0 (0)	1 (2.9)	
B	0 (0)	2 (5.7)	
C	0 (0)	2 (5.7)	

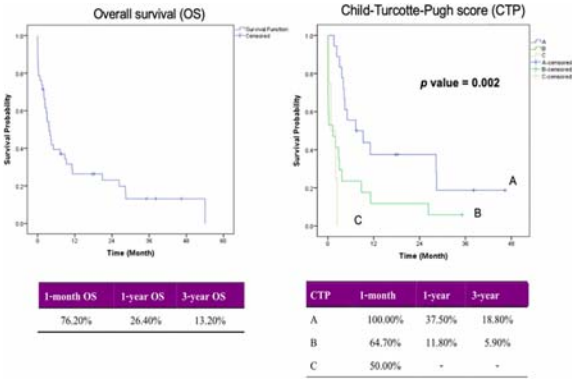

Figure 1. Overall survival (OS) of all ruptured HCC patient and OS of patient with different in CTP patient.

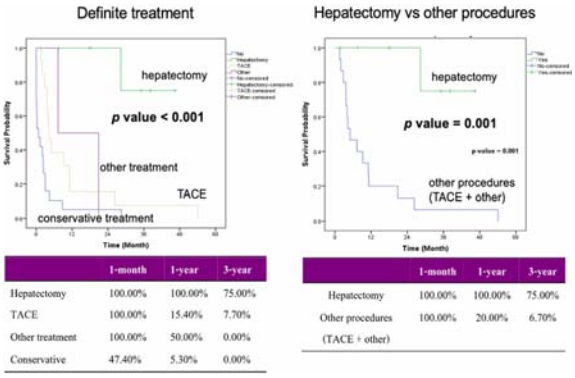

Figure 2. Overall survival (OS) in different given definite treatment in ruptured HCC patient.

13.2% at 3 years. Patients with a different CTP scores differed significantly. The survival rate in CTP-A group showed statistically significant higher to CTP-B and CTP-C group ($p = 0.002$) (Figure 1). The cumulative overall survival rates of patients receiving hepatectomy as definite treatment also differed. Patients who could undergo hepatectomy showed statistically significantly higher survival rates compared to other treatment modalities ($p<0.001$). The subgroup analysis comparing hepatectomy as definite treatment with other modalities also showed significant higher survival rate ($p = 0.001$) (Figure 2).

Discussion

The study shows the incidence of ruptured HCC is higher in males. Viral-related HCC predominate in our patients, which corresponds with the Asian scenario. CTP class A predominated in the survivor group of our study, which is not the case in a few of the recent publications where class B and C predominate[9]. This might be due to the nature of the growth rate of tumor in CTP class A is higher than other classes.

Ruptured HCC is a life-threatening complication that can cause sudden death. Its incidence has been reported to be 3 to 15% of all cirrhotic patients. HCC rupture is also a dangerous condition in the clinic with a poor prognosis; the 30-day mortality rate has been reported to range from 25% to 70%[10]. Our study showed the 1-month, 3-month and 1-year OS are 76.2%, 26.4% and 13.2%, respectively.

In the management of ruptured HCC, hemostasis

Table 4. Cox-regression of independent variables to mortality

Prognosis Factor	Univariate analysis		Multivariate analysis	
	Crude HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Age (year)	1.009 (0.987 to 1.032)	0.432		
BMI (kg/m^2)	0.965 (0.883 to 1.054)	0.427		
Blood chemistry				
Hb (g/dL)	0.737 (0.571 to 0.951)	0.019		
Platelet (/uL)	1.000 (1.000 to 1.000)	0.747		
Cr (mg/dL)	1.398 (1.1.04 to 1.770)	0.005	2.408 (1.027 to 5.645)	0.043
Total bilirubin (mg/dL)	1.047 (0.998 to 1.099)	0.062		
INR	1.032 (0.962 to 1.107)	0.384		
Blood transfusion				
PRC transfusion	1.466 (1.180 to 1.823)	0.001		
Platelet transfusion	1.070 (0.952 to 1.202)	0.257		
FFP transfusion	1.001 (1.001 to 1.001)	<0.001		
Tumor characteristics				
Size (cm.)	1.047 (0.975 to 1.124)	0.207		
Number of Tumor	1.050 (0.935 to 1.180)	0.408		
Number of ruptured Tumor	1.038 (0.943 to 1.144)	0.447		
Shock on presentation				
No	1			
Yes	1.008 (0.498 to 2.042)	0.982		
Child-Turcotte-Pugh score				
A	1			
B	2.761 (1.316 to 5.792)	0.007		
C	5.654 (1.650 to 19.371)	0.006		
Emergency treatment				
Conservative treatment	1			
Transarterial embolization	1.009 (0.490 to 2.076)	0.980		
Definite treatment				
Supportive treatment	1			
Hepatectomy	3.268 (0.74 to 14.444)	0.118		
TACE	0.097 (0.009 to 1.085)	0.058		
Other treatment modalities	1.240 (0.275 to 5.591)	0.780		
Definite treatment vs. supportive treatment				
Definite treatment	1			
Supportive treatment	4.635 (2.276 to 9.439)	<0.001		
Hepatectomy vs. other procedures (TACE + Other)				
Hepatectomy	1		1	
TACE + Other	15.468 (1.971 to 121.414)	0.009	15.485 (1.983 to 123.731)	0.01

is the primary concern and tumor treatment is subsequently considered. There are several modalities of treatment for achieving hemostasis such as TAE, surgical hemostasis, or emergency hepatectomy. To date, there has been no prospective randomized controlled trial or well-designed comparative study designed to determine the best method of hemostasis. Most evidence comes from cohort series.

The success rate of TAE for hemostasis ranges 53 to 100% with lower rate of complications and morbidities compared with surgical treatment[11]. It could be done with local anesthesia and super-selective catheterization of the relevant hepatic artery which reduces the risk of liver failure after embolization. Contraindication for TAE include portal vein thrombosis, kidney failure, liver failure, or CTP-C cirrhosis. After emergency fluid resuscitation, patients are classified as hemodynamically stable or not, and only some may be suitable for emergency bleeding control with TAE. Almost all patients without contraindication would be undergoing TAE, except patients who are hemodynamically stable with minimal blood, or prohibitively poor prognosis. As in the survivor group, only 4 of 10 patients underwent TAE, possible cause may be due to the low grade of bleeding from the tumor. However, there is no statistically significant difference in patients who have undergone TAE in both groups from this study. On the other hand, the survivor group could achieve a successfully definite hepatectomy treatment of about 90%, compared with 40% of the mortality group. The reasons are the minimal clinical bleeding from smaller size or number of tumors with lower CTP score.

Recent systematic review showed several factors associated with a worse prognosis in ruptured hepatocellular carcinoma including cirrhosis, higher CTP score, low hemoglobin level, high serum creatinine, high AFP, high total bilirubin level, HCC with portal vein invasion, and presence of shock on diagnosis[12]. In this study, the univariate analysis revealed that factors that affected mortality rate are high hemoglobin, high level of serum creatinine, high CTP score (B and C), PRC and FFP transfusions, treatment as conservative treatment or inability to undergo hepatectomy, higher levels of complication (Clavien-Dindo: III and IV), and patients with liver failure. The multivariate analysis indicates the higher serum creatinine is the only independent predictive factor for mortality.

Several studies have shown that one-stage liver resection or two-stage hepatectomy in ruptured HCC patients have better survival effects compared with other treatment methods[11,13,14]. In 2006, systematic review showed overall survival after curative resection of patients with previous ruptured HCC, at 1 year, 3 years, and 5 years, were 50 to 100%, 21 to 50%, and 15 to 33%, respectively[2]. This study demonstrates the alignment of the survival data. Our data showed overall survival at 1 month, 1 year, and 3 years are 100%, 100% and 75%, respectively. The multivariate analysis showed the patients who underwent hepatectomy achieved a better overall survival outcome with statistically significant differences compared with other definite procedures (p = 0.001).

The limitations of this study were the single institution retrospective with the weaknesses inherent to non-prospective studies. Further study in the multicenter analysis should be considered.

Conclusion

In conclusion, the parameters associated with mortality in ruptured HCC patients are the inability to undergo further hepatectomy and high serum creatinine levels. Curative hepatectomy is not contraindicated for patients with a history of ruptured HCC; it is also providing better survival outcomes, compared with other modalities of treatment.

What is already known on this topic?

Ruptured HCC is a life-threatening condition and can cause sudden death. Its prognosis is poor; the 30-day mortality rate has been reported to range from 25% to 70%. Our study showed the 1-month, 3-month and 1-year OS are 76.2%, 26.4% and 13.2%, respectively.

What this study adds?

The factors which affected mortality rates are high hemoglobin, high level of serum creatinine, high CTP scores (B and C), PRC and FFP transfusions, treatment as conservative treatment or inability to undergo hepatectomy, higher levels of complication (Clavien-Dindo: III and IV), and patients with liver failure. The multivariate analysis indicates the higher serum creatinine is the only independent predictive factor for mortality.

Potential conflicts of interest

The authors declare no conflicts of interest.

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ปัจจัยทำนายความเสี่ยงต่อการเสียชีวิตหลังได้รับการรักษาในผู้ป่วยที่มีภาวะเลือดออกเฉียบพลันในมะเร็งตับ

ประเวชย์ มหาวิทิตวงศ์, ธัชชัย เจริญศิลาวาทย์, ยงยุทธ ศิริวัฒนอักษร, สมชัย ลิ้มศรีจำเริญ, ประวัฒน์ โฆสิตะมงคล, ชุติวิชัย โตวิกกัย, เวธิต ดำรงกิตติกุล, พลสิทธิ์ แสงเสรีสถิตย์

ภูมิหลัง: ภาวะเลือดออกเฉียบพลันในมะเร็งตับเป็นสาเหตุทำให้มีอัตราการเสียชีวิตที่สูง อุบัติการณ์ของภาวะเลือดออกเฉียบพลันในมะเร็งตับของประเทศไทยพบจำนวนมาก แต่ยังขาดข้อมูลที่สำคัญอยู่ การศึกษานี้จึงมีวัตถุประสงค์เพื่อหาปัจจัยทำนายความเสี่ยงต่อการเสียชีวิตในผู้ป่วยกลุ่มนี้

วัสดุและวิธีการ: ศึกษาย้อนหลังเวชระเบียนผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นโรคมะเร็งตับที่เข้ารับการรักษาเป็นผู้ป่วยในโรงพยาบาลศิริราชตั้งแต่เดือนมกราคม พ.ศ. 2555 ถึง เดือนมิถุนายน พ.ศ. 2561 จำนวน 4,330 ราย พบว่าผู้ป่วยที่มีภาวะเลือดออกเฉียบพลันในมะเร็งตับมีจำนวน 45 รายที่เข้าเกณฑ์การศึกษานี้แบ่งเป็น 2 กลุ่ม ได้แก่ ผู้ที่ยังมีชีวิตอยู่และผู้ที่เสียชีวิต โดยเก็บรวบรวมข้อมูลทั่วไป อาการแสดง ผลการตรวจเลือด ลักษณะของมะเร็งตับ และการรักษาที่ได้รับ และนำมาคำนวณทางสถิติ เพื่อหาอัตราการเสียชีวิต และปัจจัยที่มีผลกระทบต่อการเสียชีวิต

ผลการศึกษา: ผู้ป่วยที่มีภาวะเลือดออกเฉียบพลันในมะเร็งตับจำนวน 45 ราย แบ่งเป็น 10 รายที่ยังมีชีวิตอยู่ และ 35 รายที่เสียชีวิต พบว่ามีผู้ป่วยที่ได้รับการรักษาด้วยวิธีการหยุดเลือดด้วยการใส่สายสวนเส้นเลือดแดงตับ ร้อยละ 40 ในกลุ่มที่ชีวิตอยู่ และร้อยละ 65 ในกลุ่มที่เสียชีวิต ส่วนการรักษาด้วยการผ่าตัดมะเร็งตับพบจำนวนร้อยละ 80 ในกลุ่มที่มีชีวิตอยู่ การวิเคราะห์พหุตัวแปรพบว่าปัจจัยทำนายความเสี่ยงต่อการเสียชีวิตในภาวะเลือดออกเฉียบพลันในมะเร็งตับ ได้แก่ การไม่สามารถได้รับการผ่าตัดรักษา ($p = 0.04$) และ ระดับ creatinine ในเลือดสูง ($p = 0.01$) อัตราการรอดชีวิตในผู้ป่วยที่มีภาวะเลือดออกเฉียบพลันในมะเร็งตับ ที่ 1 เดือน 1 ปี และ 3 ปี ได้แก่ ร้อยละ 76 ร้อยละ 26.4 และ ร้อยละ 13.2 ตามลำดับ อัตราการรอดชีวิตในกลุ่มที่ได้รับการผ่าตัดรักษามะเร็งตับ ที่ 1 เดือน 1 ปี และ 3 ปี ได้แก่ ร้อยละ 100 ร้อยละ 100 และ ร้อยละ 75 ตามลำดับ

สรุป: ปัจจัยทำนายความเสี่ยงต่อการเสียชีวิตในผู้ป่วยที่มีภาวะเลือดออกเฉียบพลันในมะเร็งตับได้แก่ การไม่สามารถได้รับการผ่าตัดรักษา และระดับ creatinine ในเลือดสูง ผู้ป่วยที่ได้รับการรักษาด้วยการผ่าตัดมะเร็งตับได้สำเร็จจะทำให้มีโอกาสการอยู่รอดสูงกว่า