RESEARCH ARTICLE

Risk Factors and Prognosis of Spontaneously Ruptured Hepatocellular Carcinoma in Thailand

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Abstract

Objective: Hepatocellular carcinoma (HCC) is the fatal cancer worldwide. Spontaneously Rupture remains important complication of HCC. The incidence of spontaneous HCC rupture was high in ASEAN but limited studies were reported. The aim of this study was to evaluate predictors and overall survival of ruptured HCC in tertiary care center in Thailand. **Methods:** We conducted a retrospective cohort study of HCC patients aged ≥15 years old during January 2012-January 2016 and followed up through June 2016 at Thammasat University Hospital, Thailand. All clinical information, laboratory and radiologic findings were collected from reviewing computer data base of medical records. **Results:** 333 patients had completely retrievable information. Of which, 51patients (15.3%) had spontaneous ruptured HCC. Clinical symptoms with abdominal discomfort and anemic symptoms were significantly higher in ruptured than non-ruptured HCC groups. (76.47% vs.39.36%: p<0.001, 13.73vs.0.71%, p<0.001). Furthermore, size of tumors, presences of metastasis and serum AFP>200 ng/mL were significantly higher in ruptured than non-ruptured HCC groups (10.29cm. vs. 6.47cm. p<0.001, 17.65% vs. 8.16%, p=0.034, 60.78% vs. 36.88%, p=0.001, respectively). In multivariate analysis, age, abdominal discomfort, anemic symptoms, Child-Pugh score>6 were independent risk factors of HCC rupture (OR=0.96, 95%CI=0.93-0.99, p=0.02; OR=3.47, 95%CI=1.26-9.6, p=0.016; OR=54.51, 95%CI=7.09-418.89, p<0.001; OR=2.62, 95%CI=1.09-6.31, p=0.031, respectively). 1-year and 2-year survival rates of ruptured HCC were 66.9% and 44.6% respectively. **Conclusions:** Age, abdominal discomfort, anemic symptoms and Child-Pugh score>6 might be predictive factors of spontaneous ruptured HCC. Ruptures of HCC remained a fatal disease with poor survival rate in Thailand. Appropriate treatment in early stage could be effective tool to improve the treatment outcomes

Keywords: Hepatocellular carcinoma- Ruptured- Thailand

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and leads to the third cancer-related death worldwide (El-Serag, 2011), thus remaining a significant health problem especially in Asian and sub-Saharan African countries (Pourhoseingholi and Zali, 2010; Wang et al., 2015; Loho et al., 2016; Kaneko et al., 2017; Chuncharunee and Siramolpiwat, 2017; Tunissiolli et al., 2017). In Thailand, HCC is the most common cancer in men and the third most common cancer in women (Somboon et al., 2014). The patients with HCC mostly have underlying chronic liver disease including liver cirrhosis (Bosch et al., 2005). The incidence of HCC is increasing in several developing countries, including Thailand and its dominant causes were related to hepatitis B virus, hepatitis C virus infection and alcoholic cirrhosis (Chunlertrith et al., 2000, Wiangnon et al., 2012; Liang et

al., 2013; Wanich et al., 2016).

One of the life-threatening complications of HCC is the spontaneous rupture of the tumor. Spontaneous rupture of HCC occurs in 3%-26% of all patients with HCC and the mortality rates are high approximately 32%-66.7% (Liu et al., 2001; Tan et al., 2006; Miyoshi et al., 2011). The prognosis of patients with ruptured HCC was poorer compared with those without ruptured HCC. The 1-year, 3-year and 5-year survival rates of patients with ruptured HCC were 54.2%, 35%, and 21.2%, and those of patients without ruptured HCC were 72.1%, 47.3% and 33.9% (Yeh et al., 2002). A median survival of 1.2-4 months in patients with untreated ruptured HCC was reported (Al-Mashat et al., 2002). The available treatments of ruptured HCC are hepatic resection, transcatheter arterial embolization (TAE) and conservative treatment (Rossetto et al., 2010). The most appropriate treatment is controversial and largely dependent on general conditions of the patients and

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compensation of the underlying cirrhosis (Yoshida et al., 2016). In selected patients, timely surgical resection can result in good prognosis and long-term survival (Tarantino et al., 2011). TAE, an alternative choice of treatment, can effectively induce hemostasis with success rates of 53%-100% (Yoshida et al., 2016).

However, there are few reports of predictors for spontaneous rupture of HCC and overall survival rate especially in ASEAN. Aim of this study was to evaluate predictors and overall survival of ruptured HCC in Thailand.

Materials and Methods

From January 2012 to January 2016, 371 patients were diagnosed with HCC and visited Thammasat University Hospital. Among them, 333 patients (89%) had completely retrievable information. All the clinical information, laboratory and radiologic findings of these 333 patients were successfully reviewed.

HCC was diagnosed by one typical radiologic imaging examination showing characteristic features of HCC, or two different radiologic imaging examinations to confirm characteristic features of HCC, or by histology confirmation of HCC. Ruptured HCC was diagnosed by the identification of HCC with hemoperitoneum, surrounding perihepatic hematoma, active extravasation of contrast materials, tumor protrusion from the hepatic surface, focal discontinuity of the hepatic surface or an enucleating sign from high-quality imaging (Kim et al., 2008).

The patients were divided into those with and without ruptured HCC. Data including demographics, clinical presentations, laboratory findings and overall survival were compared between 2 groups. The study was conducted according to the good clinical practice guideline and was approved by ethics committee of Thammasat University Hospital, Pathumthani, Thailand.

Statistical analysis

Continuous data were reported as mean and standard deviation, and compared by the Student t test or by the Mann Whitney U test where appropriate. Discontinuous data were reported as percentage and compared by the Chi-squared test or Fisher's exact test where appropriate. The Probability of survival curves were obtained by the Kaplan-Meier method and compared by the log-rank test. The survival period was defined as the length of time from the onset of the diagnosis of HCC to the death of the patient or the closing date of the study. The closing date for the study was June 30, 2016. Multivariate analyses were performed using Cox regression model. Differences were considered significant at 0.05. All analyses were performed by using SPSS Statistics version 23.0 (IBM Corp., Armonk, NY)

Results
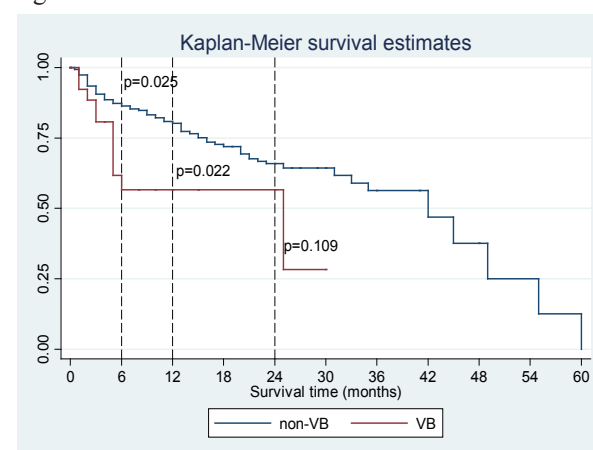
Clinical characteristics of patients

A total of 371 patients with HCC, there were 333 patients had completely retrievable information. Of the

333 patients, 79% were male and the mean age was 60 ± 12 years. Most of them (99.1%) had cirrhosis. The most common causes of chronic liver disease are HBV infection (45.9%), followed by alcohol (31.5%) and HCV infection (23.1%). 19.8% of them still had active alcohol drinking at diagnosis. Of all patients, 45% presented with abdominal discomfort, 35.1% presented with weight loss and 31.5% were asymptomatic. There were 48.9%, 45% and 5.4% of patients who had Child-Pugh A, B and C at inclusion. The mean MELD and MELD-Na scores were 11 ± 4.9 and 13.5 ± 5.7, respectively. According to BCLC staging system, HCC was diagnosed most frequently at stage B (41.7%) with the mean of the maximum size of tumors of 7.1 ± 5 cm. (from 1cm. to 22 cm.). Presence of metastasis was evident in 9.6% of all patients at diagnosis. Data are shown in Table 1.

Prevalence of ruptured HCC and comparison of patients with and without ruptured HCC

There were 51 patients out of 333 patients (16.5%) who had spontaneously rupture of HCC. Abdominal discomfort (76.47% vs. 39.36%, p<0.001), anemic symptoms (13.73% vs. 0.71%, p<0.001), peritonitis at presentation (5.88% vs. 0%, p<0.001) were more frequent in ruptured HCC groups. The mean age of patients with ruptured HCC were less than those without ruptured HCC (55.25 ± 12.16 vs. 60.73 ± 12.11 years, p=0.003). Causes of cirrhosis were not significantly different between those with and without ruptured HCC. The mean of tumor size of ruptured HCC group was significantly larger than non-ruptured HCC group (10.29 ± 5.7 cm vs. 6.47 ± 4.7 cm, p<0.001). The patients with ruptured HCC more likely to had metastatic disease at presentation (17.65% vs. 8.16%, p=0.034). The patients with ruptured HCC had more Child-Pugh B (60.78% vs. 42.5%, p=0.014) but less Child-Pugh A (31.37% vs. 52.5%, p=0.006) at presentation than those

Figure 1. Overall Survival

Time	Ruptured HCC	non-ruptured HCC	p-value
(Log- rank test)			
6 months	76.5 (61.5, 86.2)	85.2 (80, 89.2)	0.475
12 months	66.9 (50, 79.3)	80.3 (74.2, 85.1)	0.137
24 months	44.6 (23.8, 63.5)	68.4 (60.4, 75.2)	0.068

Values presented as survival probability and 95% Confident Interval (CI.). P-value corresponds to Log-rank test.

Risk Factors and Prognosis of Ruptured Hepatocellular Carcinoma

Table 1. Demographic Data of All Patients

	Total (n=333)	ruptured vs. non-ruptured HCC		
		Rupture (n=a51)	non-rupture (n=282)	p-value
Sex				
Male	263 (79%)	44 (86.27%)	219 (77.66%)	0.165
Female	70 (21%)	7 (13.73%)	63 (22.34%)	0.165
Age	59.9±12.3	55.25 ± 12.16	60.73 ± 12.11	0.003
DM	69 (20.7%)	11 (21.57%)	58 (20.57%)	0.871
Symptoms				
asymptomatic	105 (31.5%)	6 (11.76%)	99 (35.11%)	0.001*
abdominal discomfort	150 (45%)	39 (76.47%)	111 (39.36%)	<0.001*
weight loss	117 (35.1%)	17 (33.33%)	100 (35.46%)	0.77
jaundice	9 (2.7%)	1 (1.96%)	8 (2.84%)	0.723
malaise/fatigue	16 (4.8%)	3 (5.88%)	13 (4.61%)	0.696
anemic symptoms	9 (2.7%)	7 (13.73%)	2 (0.71%)	<0.001*
GI bleed	10 (3%)	0 (0%)	10 (3.55%)	0.371
fever	8 (2.4%)	1 (1.96%)	7 (2.48%)	1
Physical examination				
ascites	11 (3.3%)	4 (7.84%)	7 (2.48%)	0.049*
peritonitis	3 (0.9%)	3 (5.88%)	0 (0%)	<0.001*
hepatomegaly	1 (0.3%)	0 (0%)	1 (0.35%)	0.67
splenomegaly	2 (0.6%)	1 (1.96%)	1 (0.35%)	0.172
Cirrhosis	330 (99.1%)	50 (98.04%)	280 (99.29%)	0.384
Cause of CLD				
alcohol	105 (31.5%)	17 (33.33%)	88 (31.21%)	0.764
HBV	153 (45.9%)	25 (49.02%)	128 (45.39%)	0.632
HCV	77 (23.1%)	8 (15.69%)	69 (24.47%)	0.171
NASH	13 (3.9%)	2 (3.92%)	11 (3.9%)	0.994
cryptogenic	15 (4.5%)	2 (3.92%)	13 (4.61%)	0.827
Risk factors				
active alcohol	64 (19.8%)	11 (21.57%)	55 (19.5%)	0.734
HBeAg +ve	31/153 (20.3%)	4 (19.05%)	27 (26.73%)	0.695
antiHBe +ve	93/153 (60.8%)	18 (85.71%)	75 (74.26%)	0.203
HBV VL (cp/mL)				
≤100,000	88/153 (57.5%)	14 (66.67%)	74 (70.48%)	0.728
>100,000	38/153 (24.8%)	7 (33.33%)	31 (29.52%)	0.728
CHC S/P previous Rx	11 (3.3%)	0 (0%)	11 (16.18%)	0.152
Cure		0 (0%)	5 (45.45%)	0.338
fail		0 (0%)	6 (54.55%)	0.293
HCC BCLC stage				
A	88 (26.4%)	2 (3.92%)	86 (30.5%)	<0.001*
B	139 (41.7%)	26 (50.98%)	113 (40.07%)	0.146
C	70 (21%)	14 (27.45%)	56 (19.86%)	0.221
D	36 (10.8%)	9 (17.65%)	27 (9.57%)	0.088
Mean of max. size of mass(cm)	7.1±5 (1-22)	10.29 ± 5.7	6.47 ± 4.68	<0.001*
Major vessel thrombosis	75 (22.5%)	15 (57.69%)	60 (71.43%)	0.201
Metastasis	32 (9.6%)	9 (17.65%)	23 (8.16%)	0.034*
Child-Pugh score				
A	163 (48.9%)	16 (31.37%)	147 (52.5%)	0.006*
B	150 (45%)	31 (60.78%)	119 (42.5%)	0.014*
C	18 (5.4%)	4 (7.84%)	14 (5%)	0.403

Table 1. Continued

	Total (n=333)	ruptured vs. non-ruptured HCC		
		Rupture (n=a51)	non-rupture (n=282)	p-value
MELD score	11±4.9	11.86 ± 4.21	10.83 ± 5.05	0.171
MELD Na score	13.5±5.7	14.59 ± 5.14	13.26 ± 5.77	0.124
Signs of PHT				
ascites				
no	216 (64.9%)	24 (47.06%)	192 (68.33%)	0.004*
controlled	110 (33%)	27 (52.94%)	83 (29.54%)	0.001*
refractory	6 (1.8%)	0 (0%)	6 (2.14%)	0.293
varices	138 (41.4%)	15 (29.41%)	123 (43.77%)	0.058
splenomegaly	180 (54.1%)	23 (45.1%)	157 (55.87%)	0.163
Laboratory tests				
WBC (109/L)		8723.53 ± 4092.66	7390.43 ± 4608.74	0.054
Hct (%)		35.24 ± 7.22	51.64 ± 260.87	0.654
Plt (109/L)	183.7±110.1	226.92 ± 130.83	175.88 ± 104.32	0.002*
Cr (mg/dL)		1.19 ± 0.69	1.11 ± 0.85	0.521
AST (U/L)		187.33 ± 207.69	108.95 ± 123.47	0.011*
ALT (U/L)		82.84 ± 65.28	73.15 ± 47.76	0.315
ALP (U/L)		186.59 ± 111.78	187.95 ± 128.52	0.944
TB (mg/dL)	1.9±3.6	2.18 ± 3.35	1.82 ± 3.68	0.507
Alb (g/dL)		2.5 ± 0.55	2.43 ± 0.49	0.379
INR		1.22 ± 0.22	1.61 ± 5.98	0.644
AFP (ng/mL)				
0-20	120 (36%)	12 (23.53%)	108 (38.3%)	0.043*
20.1-200	78 (23.4%)	8 (15.69%)	70 (24.82%)	0.156
>200	135 (40.5%)	31 (60.78%)	104 (36.88%)	0.001*

Values presented as frequency (%) and mean ± SD. P-value corresponds to Independent's t test (Continuous data) and Chi square test or Fisher's exact test (Categorical data).

without ruptured HCC. The mean MELD scores were not different between 2 groups. Serum total bilirubin, INR, albumin, Creatinine were also not different between those with and without ruptured HCC. Serum AFP>200 were found more frequently in patients with ruptured HCC (60.78% vs. 36.88%, p=0.001) as in table 1.

Predictors for spontaneous rupture of HCC and Overall survival of patients

By multivariate cox'regression analysis, age, abdominal discomfort, anemic symptoms, Child-Pugh scores >6 at presentation were independently associated with spontaneously rupture of HCC (Table 2).

Overall survival of patients with ruptured HCC at 6-months, 12-month, and 42-month were 76.5%, 66.9%,

Table 2. Predictive Factors for Ruptured HCC

	Univariate analysis		Multivariate analysis	
	Crude OR	p-value	Adjusted OR (95%CI)	p-value
Male	1.81 (0.76, 4.98)	0.165		
Age	0.96 (0.94, 0.99)	0.004*	0.96 (0.93, 0.99)	0.02*
Symptoms				
abdominal discomfort	5.01 (2.43, 10.93)	<0.001*	3.47 (1.26, 9.6)	0.016*
anemic symptoms	22.27 (4, 222.79)	<0.001*	54.51 (7.09, 418.89)	<0.001*
Cirrhosis	0.36 (0.02, 21.49)	0.384		
Child-Pugh score				
B, C	2.42 (1.28, 4.57)	0.007*	2.62 (1.09, 6.31)	0.031*
Signs of PHT				
ascites	2.43 (1.33, 4.44)	0.004*	0.96 (0.43, 2.14	0.925

Values presented as Odds ratio (OR) and 95% Confident Interval (CI.). P-value corresponds to Logistic regression analysis.

44.6%, respectively. Overall survival of patients with ruptured HCC at 6-months, 12-month, and 24-month were 76.5%, 66.9%, 44.6%, respectively as shown in Figure 1..

Discussion

Spontaneous rupture of HCC is one of fatal complications of HCC leads to high mortality of 32%-66.7% (Liu et al., 2001; Tan et al., 2006; Miyoshi et al., 2011). The prognosis of patients with ruptured HCC was poorer compared with those without ruptured HCC with 1-year,3-year and 5-year survival rates of 54.2%, 35% and 21.2% vs. 72.1%, 47.3% and 33.9% in those without ruptured HCC (Yeh et al., 2002). A median survival of 1.2-4 months in patients with untreated ruptured HCC was reported (Al-Mashat et al., 2002). The primary goal of management for ruptured HCC is hemostasis control. Hemostasis could be done by TAE or surgery (Intaraprasong et al., 2016). TAE has a high success rate of 53%-100% (Yoshida et al., 2016). For the definitive treatment, staged liver resection has a good survival rate (1-year survival of 54.2%-100%; 3-year survival of 21.2%-48%; 5-year survival of 15%-21.2%) (Lai and Lau, 2006).

Still, the mechanism of spontaneous rupture is not well understood. Hypotheses include growth of tumor and necrosis, rupture by splitting of the overlying normal hepatic parenchyma or erosion of a vessel, coagulopathy leading to initiation of spontaneous bleeding within the tumor, increasing pressure within the tumor from blockage of the branches of the hepatic veins due to cancer invasion (Ong et al., 1965; Chearanai et al., 1983). Spontaneous rupture tends to occur in large tumors, but small lesions could also rupture. Suggested mechanism was that vessels in the ruptured HCC tend to be more friable due to increased collagenase expression and increased collagen IV degradation (Zhu et al., 2001; Zhu et al., 2002).

In this study, abdominal discomfort, anemic symptoms were found more frequently in patients with ruptured HCC and also independently associated with rupture of HCC which was similar to other reported series (Yeh et al., 2002; Tan et al., 2006). Patients with ruptured HCC were more likely to have extrahepatic invasion or metastasis and the mean size of tumors were was larger in ruptured HCC group (10.3±5. cm. vs. 6.5±4.7 cm.), which were also consistent with previous study (Miyosh et al., 2011; Zhu et al., 2012). Moreover, we found that the patients with ruptured HCC had more AST elevation than those without ruptured HCC, although it's not significant. This finding were reported in previous report (Yeh et al., 2002). Various mechanisms may explain more AST elevations in ruptured HCC. AST is released by damaged cells as a consequence of increased permeability of the cell membrane or cell necrosis (Yeh et al., 2002), together with some degree of hypoxic injuries that occurs after hemorrhage and more pronounced in patients with portal venous thrombosis. Although serum alpha-fetoprotein (AFP) is shown to poorly correlate with size, stage, and prognosis of HCC (Abbasi et al., 2012; Toyoda et al., 2015). However, level of >200 ng/mL was found more frequently in patients with ruptured HCC in this study.

Interestingly, age and Child-Pugh score >6 remained predictive for spontaneous rupture of HCC. However, the explanations of why younger patients with HCC more likely to have spontaneous rupture are still questionable. A few possible reasons were younger patients (mean age of 55 years) were at higher risk of unrecognized minor abdominal blunt trauma accompanied with coagulopathy might increase the risk of spontaneous HCC rupture. Child-Pugh scores>6 reflects poor liver reserve and also associated with more deficiency of clotting factors in coagulation pathway and together with platelet dysfunction (Kaul and Munoz, 2000; Tripodi et al., 2017) which consistent with previous studies that reported Child-Pugh C status was associated with poor mortality of patients with ruptured HCC (Tan et al., 2006).

In our study, the overall survival at 6 months and 12 months between patients with and without ruptured HCC was not significantly different (76.5% vs. 85.2%, p=0.475; 66.9% vs. 80.3, p=0.137, respectively). In our study, the overall survival at 6 months and 12 months between patients with and without ruptured HCC was not significantly different (76.5% vs. 85.2%, p=0.475; 66.9% vs. 80.3, p=0.137, respectively) which were comparable to previous studies (Tan et al., 2006).

There were limitations in this study. First, this was a retrospective study, it may have affected the quality of the data. Second, it was not a controlled study which possible confounding factors could occur, despite multivariate analysis was performed to decrease this effect. Third, emergency tumor resection for controlling the bleeding was a limited practice and not always an available option in our center. TAE was considered to be routinely preferred option of treatment for ruptured HCC. The cumulative survival in this study may not represent all cases with ruptured HCC, because the choice of treatment which the patients received largely influence their survival rates.

In summary, spontaneously rupture HCC is a fatal complication of HCC leading to high mortality in this group of patients. Our study demonstrated age at diagnosis, abdominal distension, anemic symptoms, Child-Pugh scores >6 were independently associated with rupture of HCC. The 24-month overall survival of those with ruptured HCC was 44.6%, significantly decreased compared with those without ruptured HCC. Since ruptures of HCC remain fatal disease with poor survival rate in Thailand, appropriate treatment in early stage could be effective tool to improve the treatment outcomes.

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