RESEARCH ARTICLE

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Clinical Outcome and Predictive Factors of Variceal Bleeding in Patients with Hepatocellular Carcinoma in Thailand

Jitrapa Kerdsuknirun[1], Virunpat Vilaichone[2], Ratha-Korn Vilaichone[1,3,4]*

Abstract

Objective: Hepatocellular carcinoma (HCC) is common cancer in ASEAN. Variceal bleeding (VB) is considered to be fatal complication of cirrhosis with HCC. However, limited studies were reported in ASEAN. Aim of this study was to evaluate overall survival rate and predictors of VB in HCC patients. **Methods:** We conducted a retrospective cohort study of HCC patients aged ≥15 years between January 2012-January 2016 and follow up through June 2016 at Thammasat University Hospital, Thailand. Clinical information and radiologic findings were collected from reviewing computer database of medical records. **Results:** 333 patients had completely retrievable information. Of which, 27 patients (8.1%) had documented with VB. Clinical presentations with weight loss and jaundice were higher in VB than non-VB groups (40.74% vs. 34.64%, p=0.525 and 7.41% vs. 2.29%, p=0.116) but the differences were not significant. The most common causes of cirrhosis in HCC patients with VB were chronic HBV infection (55.56%). In multivariate analysis; presence of ascites, Child-Pugh score>6, presence of varices were independent risk factors of having VB in HCC patients (OR=7.59, 95%CI=1.13-50.88, p=0.037; OR=5.07, 95%CI=1.08-23.76, p=0.039; OR=23.51, 95%CI=4.71-117.35, p<0.001, respectively). In HCC patients with VB, 1-year and 2.5-year survival rates were 56.6% and 28.3%. **Conclusions:** HCC patients with ascites, Child-Pugh score>6 and presence of varices might be important predictive factors of VB. Having VB were greatly impact to the survival rate of HCC patients. Clinical suspicion and regular surveillance of VB in HCC patients at risk could improve treatment outcomes.

Keywords: Hepatocellular carcinoma- variceal bleeding- Thailand

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and leads to major cancer related death worldwide (El-Serag, 2011; Kaneko et al., 2017; Chuncharunee and Siramolpiwat, 2017; Loho et al., 2016; Intaraprasong et al., 2016). 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 and alcoholic cirrhosis (Liang et al., 2013; Chunlertrith et al., 2000; Loho et al, 2016; Wiangnon et al., 2012; Wanich et al., 2016).

Variceal bleeding is one of the most serious complications of advanced cirrhosis and portal hypertension, which is considered a medical emergency and associated with significant mortality of 10-20% at 6 weeks (Graham and Smith, 1981; De Franchis, 2015). The incidence of HCC patients presenting with variceal bleeding ranging from 1%-15% (Lang et al., 2004). HCC is one of several factors that have been associated with increased mortality for an episode of variceal bleeding (D'Amico and De Franchis, 2003). The overall survival of HCC patients presenting with variceal bleeding was significantly worse than symptomatic HCC patients without VB with the median survival of 3.5 months vs. 5 months (Lang et al., 2004). The recommended management of variceal bleeding is combination of vasoactive agents and endoscopic variceal ligation (EVL) or endoscopic therapy with tissue adhesive agents depending on types of varices and considering early transjugular intrahepatic portosystemic shunt (TIPS) placement in cases with high risk of treatment failure (De Franchis, 2015). Although successful EVL significantly reduced mortality in HCC patients with VB, the overall survival was still poor in this group of patients (Chen et al., 1995,)

However, there are few reports of predictors for variceal bleeding in patients with HCC and overall survival of these patients. Aim of this study was to evaluate

*[1]Gastroenterology Unit, Department of Medicine, Faculty of Medicine, Thammasat University Hospital, [2]Patumwan Demonstration School, Srinakharinwirot University, Bangkok, [3]Gastric Cancer and Gastrointestinal Diseases Research Center, [4]Department of Medicine, Chulabhorn International College of Medicine (CICM) at Thammasat University, Pathumthani, Thailand. *For Correspondence: Vilaichone@hotmail.co.th*

predictive factors and overall survival of HCC patients with variceal bleeding 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 retrospectively 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. Variceal bleeding was defined as bleeding from an EV or GV confirmed by endoscopy or presence of a sign of recent bleed on a varix or presence of EVs with red signs and presence of blood in the stomach in the absence of another source of bleeding (Sarin et al., 2011).

The patients were divided into HCC patients with and without variceal bleeding. 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. Probability of survival curves were obtained by the Kaplan-Meier method and compared by the log-rank test. The survival period 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

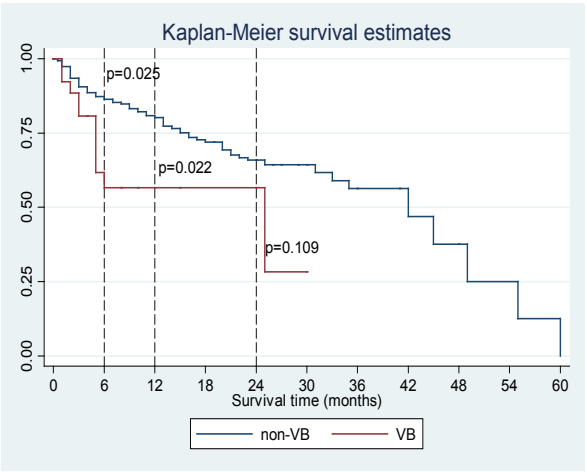
Clinical characteristics of the patients

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 59.9±12.3 years. Most of them (99.1%) had cirrhosis. The most common causes of chronic liver disease were 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 maximum size of tumors of 7.1±5 cm. (range from 1cm. to 22 cm.) as shown in table 1. Presence of major vessel thrombosis and metastasis were evident in 22.5% and 9.6% of all patients at diagnosis.

Prevalence of variceal bleeding and comparison of patients with and without variceal bleeding

There were 27 patients out of 333 patients (8.1%) who had variceal bleeding. Passing melena (25.9% vs. 1%, p<0.001), presence of ascites (14.8% vs. 2.3%, p=0.001) at presentation were more frequent in HCC with VB group. The mean age of HCC patients with and without VB were not different. Causes of chronic liver disease were not significantly different between two groups. The mean of tumor size of VB group was significantly smaller than non-VB group (5.44±3.23 cm vs. 7.2±5.14 cm, p=0.015). According to BCLC staging, the VB group had more HCC stage C (40.74% vs. 19.28%, p=0.009) and less HCC stage A (7.41% vs. 28.1%, p=0.019) than non-VB group at inclusion. The HCC patients with VB were more likely to had major vessel thrombosis at presentation (76.47% vs. 66.67%, p=0.001). Those with VB had more Child-Pugh class B (70.37% vs. 43.09%, p=0.006) and class C (14.81% vs. 4.61%, p=0.024) at inclusion than those without VB. The mean MELD scores were also higher in VB group (15.48±11.88 vs. 10.59±3.55, p=0.043). Furthermore, the patients with VB had more refractory ascites (7.41% vs. 1.31%, p=0.022), more presence of varices (88.89% vs. 37.38%, p<0.001) and sign of decompensation (22.22% vs. 9.51%, p=0.039)

Figure 1. Overall Survival of VB and non-VB Patients with HCC



Time	VB	Non-VB	p-value (Log- rank test)
6 months	56.6 (33.9, 74.2)	86.3 (81.6, 89.9)	0.025*
12 months	56.6 (33.9, 74.2)	80.2 (74.3, 84.8)	0.022*
24 months	56.6 (33.9, 74.2)	65.9 (57.9, 72.7)	0.109
30 months	28.3 (1.9, 66.7)	64.3 (55.9, 71.5)	0.066

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

Table 1. Baseline Characteristics of All Patients

	Total (n=333)	variceal bleeding vs. non-variceal bleeding		
		VB (n=27)	non-VB (n=306)	p-value
Sex				
Male	263 (79%)	25 (92.59%)	238 (77.78%)	0.07
Female	70 (21%)	2 (7.41%)	68 (22.22%)	0.07
Age	59.9±12.3	59.48 ± 11.64	59.93 ± 12.33	0.855
Symptoms				
asymptomatic	105 (31.5%)	4 (14.81%)	101 (33.01%)	0.051
weight loss	117 (35.1%)	11 (40.74%)	106 (34.64%)	0.525
jaundice	9 (2.7%)	2 (7.41%)	7 (2.29%)	0.116
malaise/fatigue	16 (4.8%)	0 (0%)	16 (5.23%)	0.223
anemic symptoms	9 (2.7%)	0 (0%)	9 (2.94%)	0.366
Physical examination				
ascites	11 (3.3%)	4 (14.81%)	7 (2.29%)	0.001*
splenomegaly	2 (0.6%)	0 (0%)	2 (0.65%)	0.674
Cause of CLD				
alcohol	105 (31.5%)	10 (37.04%)	95 (31.05%)	0.521
HBV	153 (45.9%)	15 (55.56%)	138 (45.1%)	0.296
HCV	77 (23.1%)	5 (18.52%)	72 (23.53%)	0.554
NASH	13 (3.9%)	1 (3.7%)	12 (3.92%)	0.955
HCC BCLC stage				
A	88 (26.4%)	2 (7.41%)	86 (28.1%)	0.019*
B	139 (41.7%)	9 (33.33%)	130 (42.48%)	0.355
C	70 (21%)	11 (40.74%)	59 (19.28%)	0.009*
D	36 (10.8%)	5 (18.52%)	31 (10.13%)	0.179
Mean of maximum size of mass	7.1±5 (1-22)	5.44 ± 3.23	7.2 ± 5.14	0.015*
Major vessel thrombosis	75 (22.5%)	13 (76.47%)	62 (66.67%)	0.001*
Child-Pugh score				
A	163 (48.9%)	4 (14.81%)	159 (52.3%)	<0.001*
B	150 (45%)	19 (70.37%)	131 (43.09%)	0.006*
C	18 (5.4%)	4 (14.81%)	14 (4.61%)	0.024*
MELD score	11±4.9	15.48 ± 11.88	10.59 ± 3.55	0.043*
MELD Na score	13.5±5.7	17.85 ± 11.74	13.07 ± 4.65	0.045*
Decompensation	35 (10.5%)	6 (22.22%)	29 (9.51%)	0.039*
Signs of PHT				
ascites				
No	216 (64.9%)	15 (55.56%)	201 (65.9%)	0.291
controlled	110 (33%)	10 (37.04%)	100 (32.79%)	0.645
refractory	6 (1.8%)	2 (7.41%)	4 (1.31%)	0.022*
varices	138 (41.4%)	24 (88.89%)	114 (37.38%)	<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).

more than non-VB group as demonstrate in table 1. Serum total bilirubin, INR, albumin, Creatinine, AFP were also not different between two groups of patients.

Predictors for variceal bleeding in HCC patients and Overall survival of patients

By multivariate cox' regression analysis, presence of ascites, presence of varices and Child-Pugh scores >6 (child B or C) at presentation were independently associated with variceal bleeding in HCC patients (Table 2).

Overall survival of HCC patients with variceal bleeding at 1 year and 2.5 years were 56.6% and 28.3%, respectively and were decreased significantly compared with those without variceal bleeding at 1 year (56.6% vs. 80.2%, p=0.022).

Table 2. Predictive Factors of Variceal Bleeding (VB) in HCC Patients

	Univariate analysis		Multivariate analysis	
	Crude OR	p-value	Adjusted OR (95%CI)	p-value
Male	3.57 (0.85, 31.79)	0.07		
age	1 (0.97, 1.03)	0.855		
Physical examination				
ascites	7.43 (1.47, 31.42)	0.001*	7.59 (1.13, 50.88)	0.037*
hepatomegaly	0 (0, NA)	0.766		
splenomegaly	0 (0, 22.39)	0.674		
Cirrhosis	NA (0.07, NA)	0.605		
Child-Pugh score				
A	Reference	1	Reference	1
B, C	6.38 (2.1, 25.88)	<0.001*	5.07 (1.08, 23.76)	0.039*
MELD score	1.12 (1.05, 1.2)	<0.001*	1.04 (0.83, 1.31)	0.721
MELD Na score	1.1 (1.04, 1.17)	0.001*	0.98 (0.82, 1.18)	0.828
Decompensation	2.73 (0.83, 7.72)	0.039*	0.19 (0.03,1.18)	0.075
Signs of PHT				
ascites	1.55 (0.69, 3.42)	0.283		
varices	13.47 (3.93, 70.94)	<0.001*	23.51 (4.71, 117.35)	<0.001*
splenomegaly	1.26 (0.53, 3.11)	0.571		

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

Discussion

Variceal bleeding is a vital complication of cirrhosis and associated with significant mortality of 10-20% at 6 weeks (Graham and Smith, 1981; De Franchis, 2015). The incidence of HCC patients presenting with variceal bleeding ranging from 1-15% (Lang et al., 2004). HCC is shown to associated with increased mortality for an episode of variceal bleeding (D'Amico and De Franchis, 2003). The overall survival of HCC patients presenting with variceal bleeding was significantly worse than symptomatic HCC patients without variceal bleeding with median survival of 3.5 months vs. 5 months (Lang et al., 2004). Although successful endoscopic and pharmacologic treatment significantly reduced mortality in HCC patients with variceal bleeding, the prognosis of this group of patients was grave (Chen et al., 1995).

The severity of liver disease is a well-known risk factor of variceal bleeding in patients with cirrhosis and strongly affects prognosis (D'Amico and De Franchis, 2003; del Olmo et al., 2000). In our study, HCC patients with VB were more likely to have ascites and refractory ascites than those without VB, which reflect more advance degree of portal hypertension and decompensation. We also demonstrated that HCC patients with VB more likely to have Child-Pugh scores>6 (Child B and C) and higher MELD scores than those without VB, showing that more severe cirrhosis could contribute to variceal bleeding in HCC patients, which is consistent with prior studies (Lang et al., 2004). Result of portal hypertension directly caused by underlying severe cirrhosis rather than presence of HCC per se (Chen et al., 1998). We indicated that VB group had more HCC BCLC stage C and more major vessel thrombosis than non-VB group. HCC stage C, according to BCLC, is defined by patients either have major vessel thrombosis or metastasis or both. The major vessel thrombosis especially portal vein thrombosis which could occur in HCC or advanced cirrhosis (Kinjo et al., 2014) or tumor thrombus might also contribute to increases in portal venous pressure and finally led to variceal bleeding. The size of tumor were not different between 2 groups which consistent with previous report (Lang et al., 2004).

In our study, presence of ascites, Child-Pugh scores>6 (Child B and C), presence of varices remained major predictive factors for VB in HCC patients. All reflected more severe cirrhosis and more degree of portal hypertension which undoubtedly explained VB coondition. We demonstrated the overall survival at 1 year and 2.5 years were 56.6% and 28.3%, respectively and were decreased significantly compared with those without VB at 1 year (56.6% vs. 80.2%, p=0.022). MELD scores and presence of HCC were shown to be important prognostic factors in cirrhotic patients presenting with VB (D'Amico and De Franchis, 2003; Amitrano et al., 2005). Especially, MELD >15 is associated with high mortality risk in bleeding patients (Amitrano et al., 2005).

In summary, variceal bleeding is a fatal complication of cirrhosis and HCC leading to increased mortality rate. Our study indicated that presence of ascites, Child-Pugh scores >6, presence of varices were independently associated with VB in HCC patients. The 1-year and 2.5-year cumulative survival of HCC patients with VB were 56.6% and 28.3%, respectively and were decreased significantly compared with those without VB at 1 year (55.6% vs. 80.2%). Having VB were greatly impact to the survival rate of HCC patients. Clinical suspicion and regular surveillance of VB in HCC patients at risk could

be much improved in clinical outcomes.

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