RESEARCH ARTICLE

High Prevalence of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Infection in Thailand

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Abstract

Background: Chronic hepatitis B (CHB) infection is one of the important causes of hepatocellular carcinoma (HCC) in Thailand, involved in the pathogenesis and leading to a development of HCC with or without cirrhotic changes of the liver. This study was aimed to investigate the predictive factors for HCC among CHB patients in a tertiary care center in Thailand. Materials and Methods: We conducted a retrospective study of CHB patients with or without HCC during the period of January 2009 and December 2014 at Thammasat University Hospital, Pathumthani, Thailand. Data on clinical characteristics, biochemical tests and radiologic findings were collected from review of medical records. Results: A total of 266 patients were diagnosed with CHB in Thammasat university hospital during the study period. However, clinical information of only 164/266 CHB patients (98 males, 66 females with mean age of 49.4 years) could be completely retrieved in this study. The prevalence of HCC in CHB infection in this study was 38/164 (23.2%). CHB patients with HCC had a mean age older than those without HCC (59.5 vs 47 years, P-value = 0.01). Furthermore, history of upper GI bleeding, tattooing, blood transfusion, and chronic alcoholism were significantly more common in CHB patients with HCC than patients without HCC (13.2% vs 3.2% P-value 0.03, OR = 4.6, 95%CI = 1.2-18.1, 20% vs 3.9%, P-value = 0.01, OR= 6.1, 95% CI= 1.6-23.6, 20% vs 6.3%, P-value = 0.03, OR = 3.8, 95%CI =1.1-12.7, 62.2% vs 30.3%, P-value <0.0001, OR = 3.7, 95%CI= 1.7-8.1 respectively). Interestingly, more CHB patients with HCC had evidence of cirrhosis than those without HCC (78.9% vs 20.4%, P-value <0.0001, OR = 14.6, 95%CI = 5.8-36.7). In CHB patients with HCC, surgical therapy provided longer survival than radiofrequency ablation (RFA) (72 vs 46.5 months, P-value= 0.04). The mean survival time after HCC diagnosis was 17.2 months. Conclusions: HCC remains a major problem among patients with CHB infection in Thailand. Possible risk factors are male gender, history of upper GI bleeding, chronic alcoholism, tattooing, blood transfusion and evidence of cirrhosis. For early stage HCC patients, surgical treatment provided longer survival time than RFA. Most HCC patients presented with advanced disease and had a grave prognosis. Appropriate screening of CHB patients at risk for HCC might be an appropriate approach for early detection and improvement of long-term outcomes.

Keywords: Chronic hepatitis B infection - hepatocellular carcinoma development - risk factors - Thailand.

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Introduction

Hepatocellular carcinoma (HCC) is the most frequent type of primary liver cancer and the third cancer related death worldwide (Pollack et al., 2014). Chronic hepatitis B (CHB) infection is a major public health problem and leading cause of HCC in Thailand (Somboon K et al., 2014). Approximately 400 million populations are chronically infected with hepatitis B virus. Most HCC cases are found in Asian and African people (Parkin et al., 1997, Pourhoseingholi et al., 2010).

A previous study demonstrated that CHB infection significantly increased chance of cirrhosis and HCC, which was considered as a serious cause of death worldwide (Bosch et al., 1999). Some CHB infected patients are asymptomatic but could insidiously develop to end stage liver disease and HCC. The aim of this study was to evaluate the clinical manifestations, laboratory finding, staging, and treatment outcomes of CHB patients with and without HCC in a tertiary care center in Thailand.

Materials and Methods

A retrospective study of CHB patients with or without HCC was conducted in Thammasat University Hospital, Pathumthani, Thailand between January 2009 and December 2014. All the clinical information, laboratory finding, treatment outcome and complication of eligible patients were reviewed, and relevant data were recorded into a clinical collecting form. Each variable was

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compared between CHB patients with or without HCC. The study was conducted according to the good clinical practice guideline and was approve by ethics committee of Thammasat university hospital, Pathumthani, Thailand.

Statistical analysis

All statistical analyses were performed by using SPSS Statistics version 19.0 (IBM Corp., Armonk, NY). The informationwas expressed as frequency, mean ± standard deviation (SD). Continuous variables were compared by the Student's t-test, and categorical variables were compared by Chi-square or Fisher's exact test where appropriate. The cumulative probability of mortality was computed using the Kaplan-Meier method and compared by the log-rank test. The P-values < 0.05 was considered as statistical significant.

Results

A total of 266 patients were diagnosed with CHB infection in Thammasat University Hospital during the study period. However, clinical information of 164 CHB patients (98 males, 66 females with a mean age of 49.4 years) could be achieved, and were enrolled in this study. There were 38 patients with HCC and 126 patients without HCC. Demographic data and serological tests of all patients were summarized in table 1 and table 2. The prevalence of HCC in CHB infection was 38/164 (23.2%). CHB patients with HCC had a higher mean age than those without HCC (59.5 vs 47 years, P-value = 0.01). Furthermore, history of UGI bleeding, tattooing, blood transfusion, and chronic alcoholism were significantly more common in CHB patients with HCC than patients without HCC (13.2% vs 3.2% P-value 0.03, OR = 4.6, 95%CI = 1.2-18.1, 20% vs 3.9%, P-value = 0.01, OR= 6.1, 95% CI= 1.6-23.6, 20% vs 6.3%, P-value = 0.03, OR = 3.8, 95%CI =1.1-12.7, 62.2% vs 30.3%, P-value <0.0001, OR = 3.7, 95%CI= 1.7-8.1 respectively). Interestingly, as shown in Table 1, CHB patients with HCC had evidence of cirrhosis, jaundice, hepatomegaly and ascites more common than patient without HCC (78.9% vs 20.4%, P-value <0.0001, OR = 14.6, 95%CI = 5.8-36.7;21.1 % vs7.9%, P-value = 0.02, OR = 3.1, 95%CI = 1.1-8.5; 34.2 % vs 4%, P-value<0.0001, OR =12.6, 95%CI = 4.1-38.5;

Table 1. Demographic Data for All Patients

Characteristics	CHB infection without HCC	CHB infection with HCC	P value
	-126	-38	
Sex			0.02
Male	67 (53.2%)	31(81.6%)	
Female	59 (46.8%)	7(18.4%)	
Mean age (years old)	47	59.5	0.01
Underlying diseases			
DM	11(8.7%)	7(18.4%)	0.09
HT	23 (18.3%)	9 (23.7%)	0.46
DLP	16 (12.7%)	4 (10.5%)	0.72
HIV	5 (4%)	1 (2.6%)	0.7
Route of infection			
Tattoo*	4 (3.9%)	6 (20.0%)	0.01
Blood transfusion**	6 (6.3%)	6 (20.0%)	0.03
Familial hepatitis B*	24 (23.5%)	2 (6.7%)	0.65
Alcohol drinking ***	37 (30.3%)	23 (62.2%)	<0.0001
Symptoms			
Asymptomatic	92 (73%)	12 (31.6%)	<0.0001
Abdominal discomfort	13 (10.3%)	14 (36.8%)	<0.0001
Peripheral edema	6 (4.8%)	11 (28.9%)	<0.0001
Fatigue	7 (5.6%)	2 (5.3%)	1
Anorexia	4 (3.2%)	4 (10.5%)	0.09
Upper GI bleed	4 (3.2%)	5 (13.2%)	0.03
Physical examinations			
Normal	96 (76.2%)	12 (31.6%)	<0.0001
Jaundice	10 (7.9%)	8 (21.1%)	0.02
Anemia	10 (7.9%)	6 (15.8%)	0.16
Hepatomegaly	5 (4.0%)	13 (34.2%)	<0.0001
Splenomegaly	2 (1.6%)	1 (2.6%)	0.55
Ascites	8 (6.3%)	7 (18.4%)	0.02
Cirrhosis	20 (20.4%)	28 (78.9%)	<0.0001

*N = 133, ** N = 126, *** N = 159

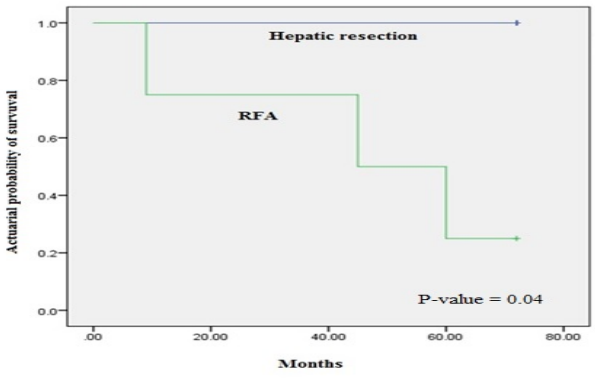

Figure 1. Actuarial Probability of Survival of HCC Patients Receiving Treatment with Hepatic Resection and RFA

Table 2. Liver Biochemical Test Data for All Patients

Serology	CHB infection without HCC	CHB infection with HCC	P value
	-126	-38	
HBsAg titer*	3,068.40 (882.1-4,272.8)	1,763.10 (826.07-4,848)	0.68
HBeAg positive**	25 (22.9%)	5 (18.5%)	0.62
Anti-HBeAg positive**	25 (75.8%)	5 (100%)	0.56
Increase AST#	44 (35.8%)	27 (71.1%)	<0.0001
Increase ALT#	50 (40.7%)	27 (55.3%)	0.11
Increase ALP#	8 (6.5%)	19 (50%)	<0.0001
Increase AFP##	9(33.3%)	23(82.1%)	<0.0001
Mean viral load cps/mL	80,592 (926.5-5,297,655)	279,360 (1,005.3-24,024,900)	0.54
Viral load > 10,000 #N	63(63%)	19(59.4%)	0.83

*N =111, **N = 136, #N = 161, ## N = 55, #N = 132

Table 3. Clinical Information and Complications of HCC Patients (n=38)

BCLC staging	Stage A (very early and early)	7 (18.4%)
	Stage B (intermediate)	24 (63.2%)
	Stage C (advance)	7 (18.4%)
Treatments	Hepatic resection	4 (10.5%)
	RFA	4 (10.5%)
	TACE	13 (34.2%)
	Palliative	10 (26.3%)
	No complication	20 (52.6%)
Complications	Ruptured hepatoma	6 (15.8%)
	Metastasis	4 (10.5%)
	Spontaneous bacterial peritonitis	6 (15.8%)
	Gastrointestinal bleeding	4 (10.5%)

18.4% vs 6.3%, P-value = 0.02, OR = 3.3, 95%CI= 1.1-9.9, respectively).For liver biochemical test, CHB patients with HCC had significantly higher number of patients who had serum AST, ALP and AFP above normal level than patients without HCC (71.1% vs 35.8%, P-value < 0.0001, OR = 4.4 95%CI= 2.0-9.7, 50% vs 6.5%, P-value < 0.0001, OR = 14.4, 95%CI = 5.5-37.5, 82.1% vs 33.3%, P-value < 0.0001, OR = 9.2, 95%CI = 2.6-32.3, respectively). In CHB patients with HCC, surgical therapy provided longer survival than radiofrequency ablation (RFA) (72 months vs 46.5 months, P-value= 0.04). The mean survival time after HCC diagnosis was 17.2 months. In HCC patients, ruptured hepatoma and spontaneous bacterial peritonitis remained common complications and were detected in 6/38 (15.8%) and 6/38 (15.8%). Clinical information and complications of HCC patients were summarized in Table 3. The survival curve for HCC patients who received curative therapy with RFA and surgical resection was shown in Figure 1

Discussion

HCC is the sixth most common cancer worldwide (Michielsen et al., 2011). Previous study in Thailand demonstrated that CHB infection is the leading cause of HCC (Somboon et al., 2014). Most of patients with HCC have a background of liver cirrhosis (Michielsen et al., 2011). However, HCC could also present in patients with CHB infection whose liver has not yet turn to be cirrhotic (Liang et al., 2013). In our study, one fifth of patients with CHB infection developed HCC without any evidence of cirrhosis. Currently, male is one of the major accepted precipitating factors of HCC (Wiangnon S et al., 2012, Taylor et al., 2009). Same as our finding, HCC was predominantly found in male in this cohort. Alcohol consumption is another direct potential factor that contributes to the development of HCC (Bosch FX et al., 1999, Pollack et al., 2014). We have also demonstrated that patient who has been an active alcohol drinker had a significantly higher chance to develop HCC than those without history of alcohol consumption. High-level of hepatitis B virus (>10,000-1,000,000 copies/ml) was strongly associated with HCC transformation (Mendy et al., 2010, Pollack et al., 2014). Interestingly, our study has shown that the incidence of patients with hepatitis B viral load >10,000 copies/ml were not different between those with and without HCC. The explanations might be possibly higher viral load cut-off required or different in host and environmental factors that might overcome the effect of high viral load. Tattooing and blood transfusion are long known risk factors of hepatitis B and C infection in Thailand (Chunlertrith et al., 2000) and we have demonstrated that these 2 factors might be related to the development of HCC.

At the present time, Barcelona Clinic Liver Cancer (BCLC) staging system is considered to be the standard guideline for HCC management worldwide. The advantage of BCLC system is that it provides patents' prognosis according to tumor size, staging and performance status, together with appropriate treatment options. This study demonstrated that most of our patients were in BCLC stage B and C, which were considered as incurable stage. Accordingly, these patients had a low chance to receive curative therapy, thus this easily explained a poor survival demonstrated in this study. On the other hand, HCC patients with BCLC stage A had a higher chance to receive curative treatment contributing to a better prognosis. RFA and surgical treatment were the main curative therapy for HCC patients in Thailand (Somboon et al., 2014). Our study demonstrated that early stage of HCC patients treated with RFA had a shorter survival time than hepatic resection. RFA is one of curable therapy, but is considered as operator dependent, requires longer procedure time to achieve complete tumor ablation, and sometimes is performed in patients who do not fit for surgery due to serious comorbid diseases.

In summary, HCC remains the major problem among patients with CHB infection in Thailand. The possible risk factors were male, history of upper GI bleeding, chronic alcoholism, tattooing, blood transfusion and evidence of cirrhosis. For early stage of HCC patients, surgical treatment provided longer survival time than RFA. Most of HCC patients presented with advanced diseases and had grave prognosis. Appropriate screening in CHB patients who are at high risk for HCC development might be an appropriate way for early detection and improvement of the treatment outcome.

References

Bosch FX, Ribes J, Borras J, et al (1999). Epidemiology of primary liver cancer. *Semin Liver Dis*, **19**, 271-85.

Chunlertrith K, Sukeepaisarnjaroen W, Mairiang P, et al (2000). Clinico-epidemiology of hepatitis C viral infection in northeastern Thailand.Southeast. Southeast *Asian J Trop Med Public Health*, **31**, 273-6.

Liang T, Chen EQ, Tang H. (2013). Hepatitis B virus gene mutations and hepatocarcinogenesis. *Asia Pac J Cancer Prev*, **14**, 4509-13

Mendy ME, Welzel T, Lesi OA, et al (2010). Hepatitis B viral load and risk for liver cirrhosis and hepatocellular carcinoma in The Gambia, West Africa. *J Viral Hepat*, **17**, 115–22.

Michielsen P, Ho E (2011). Viral hepatitis B and hepatocellular carcinoma. *Acta Gastroenteral Belq*, **74**, 4-8.

Parkin DM, Bray F, Ferlay J, et al (2005). Global cancer statistics, 2002. *CA cancer J Clin*, **55**, 74-108.

Pollack HJ, Kwon SC, Wang SH, et al (2014). Chronic hepatitis B and liver cancer risks among Asian immigrants in New

York City: Results from a large Community-Based screening evaluation and treatment program. *Cancer Epidemiol Biomarkers Prev*, **23**, 2229-39.

Pourhoseingholi MA, Fazeli Z, Zali MR, et al (2010). Burden of hepatocellular carcinoma in Iran; Bayesian projection and trend analysis. *Asia Pac J Cancer Prev*, **11**, 859-62.

Somboon K, Siramolpiwat S, Vilaichone RK (2014). Epidemiology and survival of hepatocellular carcinoma in the Central Region of Thailand. *Asian Pac J Cancer Prev*, **15**, 3567-70.

Taylor BC, Yuan JM, Shamliyan TA, et al (2009). Clinical outcomes in adults with chronic hepatitis B in association with patient and viral characteristics: A systematic review of evidence. *Hepatol*, **49**, S85-95.

Wiangnon S, Kamsa-ard S, Suwanrungruang K, et al (2012). Trend in incidence of hepatocellular carcinoma, 1990-2009, KhonKaen, Thailand. *Asian Pac J Cancer Prev*, **13**, 1065-8.