# Comparison of Clinical Features and Survival of Patients with Hepatitis B- and Hepatitis C-Associated Hepatocellular Carcinoma in Thailand

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**Abstract**

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are leading causes hepatocellular carcinoma (HCC) worldwide. The aim of this study was to determine whether differences do exist between HBV- and HCV-associated HCC in terms of clinical, pathologic features and prognosis among Thai patients. The authors retrospectively reviewed the clinical data of 188 patients with pathologically proven HCC, who were admitted to Chulalongkorn Hospital between January 1997 and December 1999. Of these cases, there were 105 patients (55.9%) with hepatitis B surface antigen (HbsAg) positive, 19 patients (10.1%) with anti-HCV positive, and 2 patients (1.0%) with both markers positive. The authors found that the mean age of patients with HBsAg positive was significantly lower than that of anti-HCV positive (49.2 ± 12.7 and 58.3 ± 8.9 years, respectively, $p = 0.003$). In contrast, the mean serum alpha-fetoprotein level of HBsAg positive group was significantly higher than that of anti-HCV positive group (48,583.6 ± 109,494.1 and 2,022.7 ± 4,869.1 IU/ml, respectively, $p = 0.001$). However, there was no difference between the two groups in terms of the severity of underlying liver disease, tumor histology and morphology, clinical staging, and the overall survival rate of the patients. The authors concluded that, among Thai populatons, the majority of clinical features and survival of HBV-associated HCC did not differ from those with HCV-associated HCC.

**Key word :** Hepatocellular carcinoma, Hepatitis B, Hepatitis C, Alpha-fetoprotein, Thailand

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Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, particularly in sub-Saharan Africa and Southeast Asia regions where its prevalence is high[1]. In Thailand, HCC represents the most common malignant tumor, with an incidence of 6.8 per 100,000 in men and 2.3 per 100,000 in women per year[2]. Various risk factors have been associated with the development of HCC, such as dietary exposure to aflatoxin, heavy alcoholic consumption and chronic infection with hepatitis viruses, in particular hepatitis B virus (HBV) and hepatitis C virus (HCV)[3]. Epidemiological studies indicate that the relative roles of these two viruses in hepatic carcinogenesis vary considerably among different populations. For example, HBV is considered a primary risk factor for HCC in China and Southeast Asia, whereas HCV plays an important role in the development of liver cancer in Japan and Europe[4]. Moreover, several recent studies have examined the clinicopathologic differences among patients with HCC infected with these two viruses. Most of these studies have shown that HCV-associated HCC occurs in older patients with more severe liver disease than those with HBV, but there is no difference between the two groups in terms of disease-free or overall survival[5-9]. These reports from Japan and Western countries, however, are not necessarily comparable with the data from Thailand where HBV-associated HCC is predominant.

The aim of the present study was, therefore, to determine whether differences do exist between HBV- and HCV-associated HCC in terms of clinical, pathologic features and prognosis among Thai patients. In this respect, the authors retrospectively reviewed the data of patients with HCC who had been admitted to our institute between January 1997 and December 1999.

## PATIENTS AND METHOD

A retrospective case review was undertaken for 219 patients with HCC consecutively diagnosed based on histopathological features at Chulalongkorn University Hospital between January 1997 and December 1999. The authors examined the patients' demographic parameters, such as sex and age, as well as clinical data including liver function test, presence or absence of cirrhosis, severity of liver disease graded as the Child-Pugh score, etiologic factors predisposing towards HCC (HBV, HCV or alcohol abuse), serum alpha-fetoprotein (AFP) level at diagnosis, degree of tumor differentiation, tumor morphology and extension, presence of vascular thrombosis; staging according to Okuda's criteria; evidence of metastases to extrahepatic regional lymph nodes or other organs; modalities of therapy of HCC including surgical resection of tumor, transcatheter arterial chemoembolization (TACE), percutaneous ethanol injection (PEI) and systemic chemotherapy. In addition, the patients' survival time was also calculated starting with the time of cancer diagnosis.

Tumor morphology and extension, as well as presence of portal vein thrombosis, were obtained by abdominal ultrasound and/or computerized tomography (CT). According to the Cancer of the Liver Italian Program (CLIP)[10], the tumor morphology and extension of HCC were categorized into 3 groups as follows: group 1 uninodular and extension $\leq 50$ per cent, group 2 multinodular and extension $\leq 50$ per cent, and group 3 massive or extension $> 50$ per cent.

Hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (anti-HCV) and AFP level were determined by enzyme-linked immunosorbent assays (ELISA) for detection of HBsAg (Auszyme II, Abbott Laboratories, North Chicago, IL), anti-HCV (ELISA II; Ortho Diagnostic Systems, Chiron Corp., Emeryville, CA) and AFP (Cobus® Core, Roche Diagnostics, Basel, Switzerland). Liver function tests [serum levels of bilirubin, akaline phosphatase, transaminase (AST, ALT) and albumin levels] were determined by the central laboratory, Chulalongkorn Hospital.

### Statistical analysis

Data were presented as percentage, mean and standard deviation. The Chi-square, ANOVA and unpaired *t*-test were used to assess the statistical significance of the difference between groups as appropriate. Survival curves were constructed using the Kaplan-Meier method and differences between curves were tested using the log-rank test using SPSS software (SPSS Inc., Chicago, IL). A p-value of less than 0.05 was considered statistically significant.

## RESULTS

After reviewing the patients' medical records, 31 cases were excluded from this study due to incomplete clinical data. Of 188 patients remaining for the analysis, they comprised 162 males and 26 females with their ages ranging from 19 to 95 years (mean 53.1 ± 12.6 years). Upon categorization based on serum HBsAg and anti-HCV, there were 105 patients (55.9%) with HBsAg positive, 19 patients (10.1%) with anti-HCV positive, 2 patients (1.0%) with both

markers positive, and 62 patients (33%) with both markers negative (31 patients had a previous history of heavy alcoholic consumption and the etiology was not known in the remaining 31 patients).

To determine if clinico-pathologic differences exist between HBV- and HCV-associated HCC, the authors further compared the data of 105 patients with HBsAg positive and 19 patients with anti-HCV positive. As shown in Table 1, the mean age of patients who were HBsAg positive was significantly lower than that of the anti-HCV positive groups (49.2 ± 12.7 and 58.3 ± 8.9 years, respectively, p = 0.003). In contrast, the mean serum AFP level of HBsAg positive group was significantly higher than that of the anti-HCV positive group (48,583.6 ± 109,494.1 and 2,022.7 ± 4,869.1 IU/ml, respectively, p = 0.001). However, no significant differences between groups were observed regarding biochemical abnormalities and the severity of underlying liver disease according to the Child-Pugh score. Likewise, no significant differences between groups were observed as to the degree of tumor differentiation, tumor morphology and extension, clinical staging according to Okuda's criteria, the presence of portal thrombosis, extrahepatic metastasis, and therapeutic modalities (Table 2).

Kaplan-Meier survival curves demonstrated that the median survival rates for patients with HBsAg positive and anti-HCV positive were 6.0 and 5.5 months, respectively (Fig. 1). However, there was no

**Table 1. Demographic and clinical data of HCC patients with respect to HBsAg and anti-HCV.**

| Characteristics | HBsAg positive | Anti-HCV positive | P |
|---|---|---|---|
| No. of patients | 105 | 19 | |
| Sex (Male : Female) | 92 : 13 | 15 : 4 | NS |
| Age (years) | 49.2 ± 12.7 | 58.3 ± 8.9 | 0.003 |
| Heavy alcoholic intake (+ : -) | 20 : 85 | 3 : 16 | NS |
| Child's classification (A : B : C) | 64 : 34 : 5 | 9 : 8 : 2 | NS |
| Biochemical liver function tests | | | |
| Total Bilirubin (mg/dl) | 3.3 ± 6.4 | 3.5 ± 7.0 | NS |
| Alkaline phosphatase (IU/L) | 538.9 ± 405.9 | 451.7 ± 349.9 | NS |
| AST (IU/L) | 178.7 ± 158.5 | 166.4 ± 101.1 | NS |
| ALT (IU/L) | 92.5 ± 96.2 | 106.4 ± 79.5 | NS |
| Albumin (g/dl) | 3.3 ± 0.5 | 3.3 ± 0.6 | NS |
| Prothrombin time (sec) | 14.3 ± 2.4 | 13.6 ± 1.4 | NS |
| Mean AFP (IU/ml) | 48,583.6 ± 109,494.1 | 2,022.7 ± 4,869.1 | 0.001 |

Quantitative variables were expressed as mean ± SD, (+ : -) = positive : negative.

**Table 2. Clinicopathologic data of HCC patients with respect to HBsAg and anti-HCV.**

| Characteristics | HBsAg positive | Anti-HCV positive | P |
|---|---|---|---|
| Tumor cell differentiation (Well : Moderately : Poorly) | 5 : 35 : 16 | 1 : 5 : 3 | NS |
| Tumor morphology (Uni : Multi : Mass) | 32 : 60 : 13 | 8 : 8 : 3 | NS |
| Okuda' s staging (I : II : III) | 19 : 74 : 12 | 3 : 14 : 2 | NS |
| Portal vein thrombosis (+ : -) | 31 : 74 | 9 : 10 | NS |
| Extrahepatic metastasis (+ : -) | 17 : 88 | 4 : 15 | NS |
| Therapy for HCC (+ : -) | 46 : 55 | 10 : 9 | NS |
| Modality of therapy | | | NS |
| Surgery (+ : -) | 18 : 87 | 2 : 17 | |
| Chemoembolization (+ : -) | 15 : 90 | 6 : 13 | |
| Chemotherapy (+ : -) | 8 : 97 | 1 : 18 | |
| More than 1 modality (+ : -) | 5 : 100 | 1 : 18 | |

(+ : -) = positive : negative, Uni = uninodular and extension ≤ 50 per cent,
Multi = multinodular and extension ≤ 50 per cent, Mass = massive or extension > 50 per cent

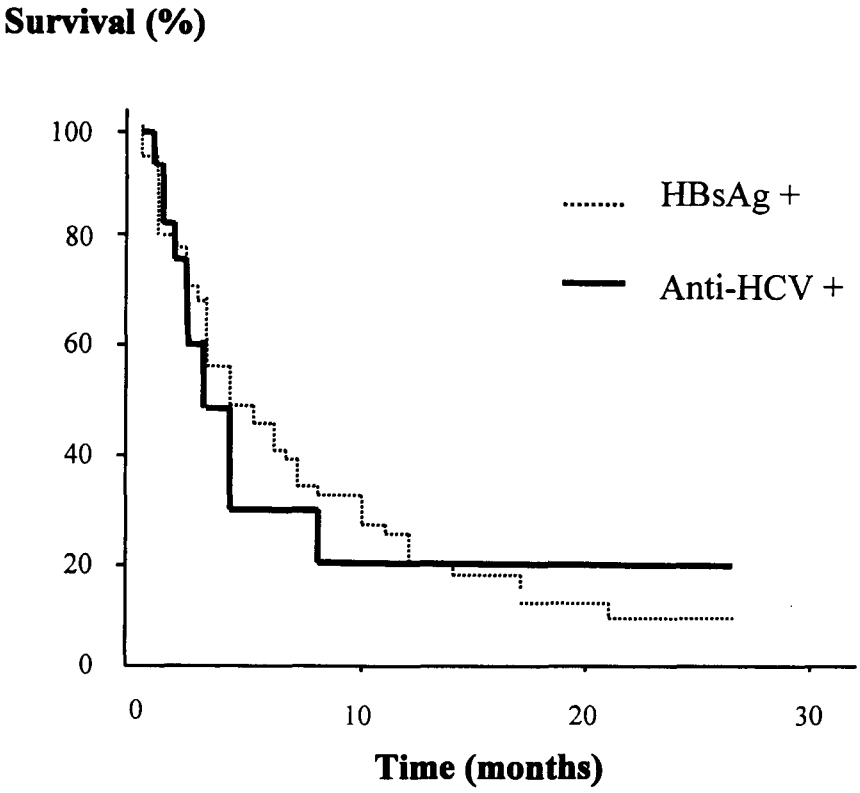


**Fig. 1. Overall survival of patients with HCC with reference to HBsAg and anti-HCV.**

significant difference in the median survival between groups by using the log-rank method (p = 0.54, 95% confidence interval 0.50-2.75).

## DISCUSSION

The present study has shown that in Thailand, as in other countries in the Far East and Southeast Asia[11], HCC frequently develops in individuals with pre-existing chronic HBV infection. The positive HBsAg status was prevalent in approximately 60 per cent of cases, and was almost six times exceeded that of chronic HCV infection. Indeed, chronic HBV infection is considered the most common etiologic factor in the development of HCC worldwide, accounting for 1 million deaths annually[12]. Previous studies have demonstrated that simultaneous infections with HBV and HCV might accelerate the clinical progression of chronic hepatitis to cirrhosis and HCC, and such dual infections were found in approximately 10 per cent of HCC patients in HBV-endemic areas[13]. Based on the presented data, however, HBV-HCV coinfections were much less prevalent (approximately 1%) than generally documented, suggesting the dual infections might play a negligible if any role in the development of HCC among Thai populations. On the other hand, the absence of serological markers of either HBV or HCV infection cannot completely rule out a viral etiology of hepatocarcinogenesis as virus replication may persist in the hepatic tissue despite undetectable markers in serum[14].

In the current study, the authors found that the mean age of patients who were HBsAg positive was significantly younger than that of anti-HCV positive cases. This observation was in agreement with previous reports that the mean age differences of 5 to 10 years can be identified between HBV- and HCV-associated HCC (usually approximately 55 *versus* 65

years old)[15]. The age discrepancy might reflect the different mode of transmission and time of exposure between HBV and HCV infections among Thai populations. For HBV, it is believed that most infections are acquired by vertical (perinatal) and early horizontal (within extended families) transmissions. In contrast, most HCV infections result from direct percutaneous exposure such as bloodborne contact, which generally occurs after adolescence. Moreover, in the majority of patients the interval between exposure to HCV and HCC development is long, being estimated at approximately 30 years[16].

Regarding etiologic factors of HCC affecting AFP levels, the authors found that higher AFP levels tended to be more frequently detected in HBV-associated HCC than HCV-related cases. AFP belongs to a group of plasma proteins called feto-specific proteins normally synthesized by the fetal yolk-sac during early embryonic life and later by fetal liver cells but produced at a very low level or altogether undetectable in healthy adults. Raised serum AFP concentrations are present in the majority, but not all, of patients with HCC. Furthermore, increase in serum AFP is not specific to HCC because it can be raised in a variety of malignant and non-malignant conditions such as chronic hepatitis, cirrhosis and fulminant hepatic failure[17]. The mechanism of increased serum AFP levels in HCC is thought to result from overexpression of the AFP gene in the tumor cells[18]. However, the explanation of the difference between HBV and HCV as to enhancing AFP expression in the present study is unclear, but this might be related to the different mechanisms of hepatocarcinogenesis. Unlike HCV that is not integrated into the host genome, HBV DNA integration in the course of chronic infection could result in increased HBxAg expression. The HBxAg on its part has been shown capable of activating the 5'-upstream sequence of the alpha-fetoprotein gene *via* the CAAT enhancer binding protein (C/EBP) site, resulting in elevation of serum AFP levels[19]. Indeed, HBxAg appears to be a potent transactivator predominantly acting on transcription factors, thereby allegedly inactivating negative growth-regulatory genes, such as the tumor suppressor p53, while at the same time activating proto-oncogenes that eventually leads to malignant transformation and the development of HCC[20].

Previous data from Japan and Western countries have demonstrated that HCC developing after HCV infection exhibit more severe histological grading of liver disease than those from HBV infection (5-9). Moreover, HCV-associated liver cancers have a higher incidence of multicentricity than those positive for HBsAg[5]. These results could be attributed to the differences in the sequelae of chronic hepatitis B and C. In chronic hepatitis B, resolution of the disease is frequently found after the inactivation of viral replication, whereas in chronic hepatitis C, resolution is found in few cases and the disease tends to progress toward a more advanced stage[21]. Instead, in the present study the authors observed no difference between HBV- and HCV-associated HCC in terms of tumor histology, morphology and extension, as well as the severity of the underlying liver disease. In agreement with previous reports, the prognosis of HBsAg-positive HCC did not differ from that of anti-HCV-positive cases.

In conclusion, the presented data demonstrated that HBV-associated HCC occurred in younger patients and exhibited higher mean serum AFP levels than HCV-associated HCC. Nonetheless, there was no difference between the two groups in terms of the severity of underlying liver disease, tumor histology and morphology, clinical staging, and the overall survival rate of the patients.

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# การศึกษาเปรียบเทียบลักษณะทางคลินิกและการอยู่รอดของผู้ป่วยโรคมะเร็งตับที่มีสาเหตุจากไวรัสตับอักเสบบีและไวรัสตับอักเสบซีในประเทศไทย

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ไวรัสตับอักเสบบีและไวรัสตับอักเสบซีเป็นสาเหตุสำคัญของมะเร็งตับชนิด hepatocellular carcinoma (HCC) การศึกษานี้มีจุดประสงค์เพื่อเปรียบเทียบความแตกต่างทางคลินิกและการพยากรณ์โรคของมะเร็งตับที่เกิดจากไวรัสทั้งสองชนิดนี้ โดยได้ทำการศึกษาย้อนหลังในผู้ป่วยจำนวน 188 รายที่ได้รับการวินิจฉัยทางพยาธิวิทยาว่าเป็นมะเร็งตับในโรงพยาบาลจุฬาลงกรณ์ตั้งแต่เดือนมกราคม 2540 ถึงเดือนธันวาคม 2542 การศึกษาพบว่าผู้ป่วยมีไวรัสตับอักเสบบี (ตรวจพบ HBsAg) จำนวน 105 ราย (ร้อยละ 55.9) มีไวรัสตับอักเสบซี (ตรวจพบ anti-HCV) จำนวน 19 ราย (ร้อยละ 10.1) และมีไวรัสทั้งสองชนิดจำนวน 2 ราย (ร้อยละ 1.0) ผู้ป่วยที่มีไวรัสตับอักเสบบีมีอายุเฉลี่ยต่ำกว่าผู้ป่วยที่มีไวรัสตับอักเสบซี (49.2 $\pm$ 12.7 และ 58.3 $\pm$ 8.9 ปี ตามลำดับ $p = 0.003$) แต่มีระดับค่าเฉลี่ยของ alpha-fetoprotein ในเลือดสูงกว่าอย่างมีนัยสำคัญ (48583.6 $\pm$ 109494.1 และ 2022.7 $\pm$ 4869.1 IU/ml ตามลำดับ $p = 0.001$) อย่างไรก็ตามผู้ป่วยทั้งสองกลุ่มไม่มีความแตกต่างกันในด้านอื่น ๆ เช่น ความรุนแรงของตับแข็ง ลักษณะความรุนแรงทางพยาธิวิทยาของมะเร็งตับ ลักษณะทางคลินิก และระยะความรุนแรงของโรคมะเร็งตับ ตลอดจนระยะเวลาของการอยู่รอดของผู้ป่วยหลังการวินิจฉัยโรค จากการศึกษานี้สรุปได้ว่าผู้ป่วยไทยที่เป็นมะเร็งตับจากไวรัสตับอักเสบบีมีลักษณะส่วนใหญ่ทางคลินิกและการอยู่รอดไม่แตกต่างจากผู้ป่วยที่มีไวรัสตับอักเสบซี

**คำสำคัญ** : มะเร็งตับ, ไวรัสตับอักเสบบี, ไวรัสตับอักเสบซี

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