Older Age and High A-fetoprotein Predict Higher Risk of Hepatocellular Carcinoma in Chronic Hepatitis B-Related Cirrhotic Patients Receiving Nucleos(T)ide Analogue Therapy: A Retrospective Cohort Study

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Research Article

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Abstract

Background: Nucleos(t)ide analogues (NUCs) were proved to reduce hepatocellular carcinoma (HCC) development in patients with chronic hepatitis B (CHB) infection, but data was limited on the efficacy in the CHB patients with cirrhosis.

Methods: We retrospectively analyzed data from 447 patients with CHB-related cirrhosis, who initiated tenofovir/entecavir therapy during April 2007 and August 2013. They were divided into HCC (n=48) and non-HCC (n=399) groups. The mean follow-up period was 63.2 ± 34.2 months.

Results: Forty-eight patients (10.7%) developed HCC during surveillance. The annual incidence rate of HCC was 2.04 (95% CI: 1.52–2.68) per 100 person-year. The cumulative incidence of HCC was 0.9%, 9.8% and 22.1% at the 1, 5 and 10 years, respectively. Significant predictors for HCC identified using multiple Cox regression analysis were age ≥ 50 years (hazard ratio [HR]: 2.34, 95% confidence interval [CI] = 1.08–5.1) and α-fetoprotein (AFP) ≥ 8 ng/ml (HR: 2.05, 95% CI = 1.1–3.84). The incidence rate of HCC was further analyzed in subgroups according to the risk factors identified by multivariate Cox regression. The incidence rate of HCC was 8.67-fold higher in patients with age ≥ 50 years and AFP ≥ 8 ng/ml (3.14 per 100 person-year, 95% CI = 1.99–4.72) than those with age <50 years and AFP <8 ng/ml (0.36 per 100 person-year, 95% CI = 0.06–1.19).

Conclusion: The cirrhotic CHB patients with age <50 years and AFP <8 ng/ml have the lowest annual incidence of HCC. However, the cirrhotic patients with age ≥50 years or/and AFP ≥8 ng/ml have significantly higher risk for HCC and warrant careful surveillance schedule for HCC development.

Introduction

Hepatocellular carcinoma (HCC), accounts for most of liver cancer, is the sixth most common cancer in the world. It is also the third leading cause of cancer-related mortality, causing more than 800,000 death per year (1, 2). Chronic hepatitis B virus (HBV) infection causes global health problem and more than 240 million people have the disease (3). Without treatment, 40% of the chronically infected patients will progress to cirrhosis, which increases the risk of HCC. Chronic HBV infection is also the most common cause of HCC and is associated with more than 50% of HCC cases (4, 5). Long-term therapy with nucleos(t)ide analogs (NUCs) has been well demonstrated to result in improvement of liver necroinflammation and fibrosis, and regression of cirrhosis (6–9). The risk of HCC development was also reported to be reduced significantly in the NUCs-treated patients with advanced fibrosis or cirrhosis. The risk reduction was more prominent in patients with maintained viral suppression than in those with a virological breakthrough (10–12). Because of low drug resistance rate and high potency of viral suppression, entecavir (ETV) and tenofovir disoproxil fumarate (TDF) have become the first-line NUC regimen for CHB treatment. Previous studies have shown that antiviral therapy with ETV reduce the risk of HCC in cirrhotic patients, particularly among those with maintained viral suppression. (12). The rate of
reduction of HCC incidence was also more in the ETV-treated than those with LAM-treated cirrhotic patients (13). However, the risk of HCC is not completely eliminated by NUCs therapy.

The long-term use of NUCs therapy for cirrhotic CHB patients was reimbursed by the Taiwan's national health insurance system since 2010. There are few studies focusing on assessing the predictors of on-treatment HCC development in CHB-related cirrhotic patients with NUCs therapy. Therefore, this retrospective study was conducted to elucidate the risks and predictors of HCC development during NUCs therapy, and to identify high-risk patients that warrant intensive surveillance during therapy.

**Methods**

**Study population**

The patients diagnosed with CHB-related cirrhosis and initiated long-term ETV monotherapy (0.5 mg daily) or TDF monotherapy (300 mg) in our liver research unit during April 2007 and August 2013 were enrolled in this study. Chronic HBV infection was defined as being seropositive for HBsAg for more than 6 months. Baseline clinical and biochemical data were recorded on the initiation of ETV or TDF therapy. Diagnosis of liver cirrhosis was made by liver biopsy specimen with an Ishak modified histology activity index score $\geq 5$ or Metavir score =4, or ultrasonography using the previously described cirrhosis scoring system (14) with splenomegaly or esophageal/gastric varices. All patients had serum HBV DNA $\geq 2000$ IU/ml at baseline. Patients with HCC diagnosed before and within six months after the beginning of therapy or with a follow up duration less than 6 months were excluded from the study. We also excluded CHB patients coinfected with chronic hepatitis C or human immunodeficiency virus, toxic hepatitis, autoimmune hepatitis, primary biliary cirrhosis, or Wilson's disease. This study was approved by the Medical Ethics Committee of Chang Gung Memorial Hospital (Institutional Review Board approval number: 104_9790B), and was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Follow-up for HCC surveillance**

All patients were observed from the beginning of the NUCs therapy to the date of HCC diagnosis, last-visit or death. Liver ultrasonography and laboratory examination were routinely checked every three months. The diagnosis of HCC was confirmed by the histological evaluation of a needle biopsy sample or surgically resected specimens, two typical image studies such as dynamic liver computed tomography or magnetic resonance imaging, or one image study plus an increased serum AFP level of more than 400 ng/ml (15).

**Statistical analysis**

The continuous variables were reported as mean ± standard deviation. The categorial variables were summarized as a number (percentage). The difference between continuous and categorical variables was compared using the Student $t$ test and the chi-square test. Cox proportional hazards regression
model was used to assess the clinical, biochemical and virological variables associated with the risk of HCC development. The cumulative incidence of HCC was evaluated using the Kaplan−Meier method and compared with log-rank test. All statistical tests were two-tailed, with P values <0.05 considered statistically significant. Data were analyzed using SPSS 23 software for Windows (SPSS, Inc, Chicago, IL).

Results

Patient characteristics

There was a total of 457 CHB patients with cirrhosis enrolled in our study. Six patients receiving ETV therapy and 1 patient receiving TDF therapy with a follow up duration less than 6 months, and 3 patients with HCC development within the first 6 months enrollment were excluded. Finally, 447 patients were included in our final analysis. They were divided into HCC (n = 48) and non-HCC (n = 399) groups. The baseline clinical and biochemical data of the patients on initiation of the NUC therapy was presented in Table 1. The mean age of the cirrhotic patients at initiation of NUC therapy was 55.3 ± 11.6 years, and 339 (75.8%) patients were men. Patients with HCC development during NUC therapy had lower pretreatment serum aspartate aminotransferase and higher HBV DNA levels. There was also a high percentage of patients exhibited a baseline AFP level ≥ 8 ng/ml.
Table 1
Baseline characteristics of cirrhotic chronic hepatitis B patients with and without hepatocellular carcinoma

| Baseline parameters                                      | HCC (n = 48) | Non-HCC (n = 399) | P value |
|----------------------------------------------------------|--------------|-------------------|---------|
| Age ≥ 50 years                                           | 38 (79%)     | 263 (66%)         | 0.063   |
| Gender (male)                                            | 40 (83%)     | 299 (75%)         | 0.199   |
| Body mass index (kg/m²)                                  | 24.2 ± 4.3   | 25.4 ± 4.0        | 0.06    |
| Albumin (g/dl)                                           | 3.8 ± 0.7    | 3.9 ± 0.6         | 0.231   |
| AST (U/L)                                                | 75 ± 52      | 96 ± 125          | 0.036   |
| ALT (U/L)                                                | 87 ± 77      | 109 ± 169         | 0.383   |
| Total bilirubin (mg/dl)                                  | 1.4 ± 0.8    | 1.5 ± 2.0         | 0.841   |
| AFP ≥ 8 ng/ml                                            | 29 (60%)     | 168 (42%)         | 0.016   |
| HBV DNA (log₁₀ IU/ml)                                    | 6.1 ± 1.5    | 5.5 ± 1.5         | 0.047   |
| White blood cells (x10³/µl)                              | 5.7 ± 1.8    | 6.1 ± 2.4         | 0.323   |
| Hemoglobin level (g/dl)                                  | 13.3 ± 2.6   | 13.1 ± 2.3        | 0.673   |
| Platelet count (x10³/µl)                                 | 125.5 ± 52.3 | 142.9 ± 65.8      | 0.112   |
| Creatinine (mg/dl)                                       | 0.9 ± 0.5    | 1.0 ± 1.0         | 0.568   |
| Estimated GFR (MDRD)                                     | 113.4 ± 115.1| 117.6 ± 41.1      | 0.427   |
| Fatty liver                                              | 11 (23%)     | 66 (17%)          | 0.269   |
| Ascites history                                          | 6/47 (12.8%) | 54 (13.5%)        | 0.568   |
| Variceal bleeding history                                | 5/47 (10.6%) | 31 (7.8%)         | 0.495   |
| NUCs (entecavir)                                         | 41 (85%)     | 318 (80%)         | 0.347   |

**Cumulative incidence of HCC**

The median follow-up period was 62.1 months (range: 6.1–144.6 months). Forty-eight patients (10.7%) developed HCC during surveillance period with an incidence rate of 2.04 (95% CI: 1.52–2.68) new HCC case per 100 person per year. As shown in Fig. 1, the cumulative incidence of HCC was 0.9%, 9.8% and 22.1% at the 1, 5 and 10 years, respectively.
Risk Factors Associated With HCC Development

Factors associated with risk of HCC development were assessed by the Kaplan–Meier method and compared by the log-rank test (Fig. 2). Patients with HCC development during NUC therapy were significantly older (age ≥ 50 years) (P = 0.026), had higher pretreatment serum HBV DNA levels (≥ 4 x 10^5 IU/mL) (P = 0.036), and AFP levels (≥ 8 ng/ml) (p = 0.004), and lower albumin levels (< 3 g/dl) (P = 0.033). However, different NUCs did not affect the risk of HCC development.

Baseline clinical and biochemical factors identified through univariate Cox regression analysis were then entered into stepwise multiple regression analysis. The results of multivariate Cox regression analysis showed treatment age ≥ 50 years (HR: 2.34, 95% CI = 1.08–5.1) and AFP ≥ 8 ng/ml (HR: 2.05, 95% CI = 1.1–3.84) were significant independent predictors of HCC development during NUC treatment (Table 2).

### Table 2

| Parameters                        | Univariate model | Multivariate model |
|-----------------------------------|------------------|--------------------|
|                                   | HR (95% CI)      | P Value            | HR (95% CI)      | P Value            |
| Age (years) (≥ 50 vs. <50)        | 2.17 (1.08–4.36) | 0.03               | 2.34 (1.08–5.1)  | 0.032               |
| Gender (male vs. female)          | 1.69 (0.79–3.62) | 0.175              |
| Body mass index (kg/m^2)          | 0.93 (0.86-1.0)  | 0.056              |
| HBV DNA (≥10^5 IU/ml) (≥ 4 vs. <4)| 1.96 (1.03–3.74) | 0.004              |
| Albumin (g/dl) (< 3 vs. ≥3)       | 2.91 (1.04–8.15) | 0.042              |
| AST (U/L)                         | 1.0 (0.99-1.0)   | 0.26               |
| ALT (U/L)                         | 1.0 (0.99-1.0)   | 0.268              |
| Total bilirubin (mg/dl)           | 0.99 (0.8–1.22)  | 0.9                |
| AFP (ng/ml) (≥ 8 vs. <8)          | 2.29 (1.28–4.1)  | 0.005              | 2.05 (1.1–3.83)  | 0.025               |
| Hemoglobin level (g/dl)           | 1.0 (0.81–1.24)  | 1.0                |
| Platelet count (×10^3/µl)         | 1.0 (0.99-1.0)   | 0.22               |
| Creatinine (mg/dl)                | 0.91 (0.53–1.55) | 0.73               |
| Estimated GFR (MDRD)              | 1.0 (0.99-1.0)   | 0.16               |
| Splenomegaly (yes vs. no)         | 0.72 (0.38–1.34) | 0.3                |
| Variceal bleeding episode (yes vs. no) | 1.52 (0.6–3.84) | 0.38               |
The analysis of incidence rate of HCC development was then stratified into subgroup according to the risk factors identified by multivariate analysis (Table 3). As compared to the patients with treatment age < 50 years and AFP < 8 ng/ml (0.36, 95% CI = 0.06–1.19), the incidence rates of HCC per 100 person-years were significantly higher in patients with age ≥ 50 years and AFP ≥ 8 ng/ml (3.14, 95% CI = 1.99–4.72), P = 0.004. The patients with age ≥ 50 years and AFP ≥ 8 ng/ml had 8.67-fold higher rate of HCC than those with age < 50 years and AFP < 8 ng/ml. Among patients with either age ≥ 50 years or AFP ≥ 8 ng/ml, the incidence rates of HCC was also higher than those with age < 50 years and AFP < 8 ng/ml.

Table 3

| Hepatocellular carcinoma | Events (n) | Observation Period (Person-years) | Rate/100 person-years (95% CI) | P Value |
|--------------------------|-----------|----------------------------------|------------------------------|---------|
| All                      | 48        | 2352.8                           | 2.04 (1.52–2.68)             |         |
| Age ≥ 50 years vs. AFP ≥ 8 ng/ml | 21 | 669.2                           | 3.14 (1.99–4.72)         | 0.004   |
| Age ≥ 50 years vs. AFP < 8 ng/ml | 17 | 841.8                           | 2.02 (1.22–3.17)         | 0.022   |
| Age < 50 years vs. AFP ≥ 8 ng/ml | 8    | 287.9                           | 2.78 (1.29–5.28)          | 0.01    |
| Age < 50 years vs. AFP < 8 ng/ml | 2    | 553.9                           | 0.36 (0.06–1.19)         |         |

Discussion

In the present study, we demonstrated that long-term NUC therapy could not fully eliminate the risk of HCC development in CHB-related cirrhotic patients. Age and AFP were identified to be predictors associated with HCC development. From previous studies, the cumulative incidence of HCC at year 5 was 7–18% in NUC-treated cirrhotic patients (12, 13, 16–18). Our data showed similar results that the 5-year cumulative incidence of HCC was 9.8% with an annual incidence of 2.04 per 100 person-year.

The risk factors associated with HCC development in CHB-related cirrhotic patients under NUC therapy, including older age, male gender, HBeAg positivity, statin use, platelet count, AFP and hemoglobin levels, variceal bleeding history, and 1-year virological response, had been reported by previous studies (19–21). Our study demonstrated that an older age (≥ 50 years) and AFP ≥ 8 ng/ml were predictors for risk of HCC in those patients with long-term NUCs treatment. Previous reports have indicated that the risk of HCC in cirrhotic patients under NUC therapy was age-dependent (19–21). Tsai et al. proved that a higher risk for HCC development manifested at age 60 or higher. In our study, we showed that age ≥ 50 years was a predictor for HCC development. Serum AFP was determined as a serological biomarker for detection of HCC; therefore, it has commonly been used for HCC surveillance (22, 23). A randomized controlled trial of
surveillance among CHB patients has indicated the sensitivity and specificity of AFP level to detect HCC were 64% and 91%, respectively, using a serum cut-off point of 20 ng/ml (24). In our study, the incidence rates of new HCC case per 100 person-year were significantly higher in patients with AFP ≥ 8 ng/ml (3.03, 95% CI = 2.07–4.3) than to those with AFP < 8 ng/ml (1.36, 95% CI = 0.84–2.09), P = 0.007. The patients with AFP ≥ 8 ng/ml had a 2.19-fold rate of HCC than those with AFP < 8 ng/ml. For further analysis of the risk for HCC affected by the predictors, we stratified the patients into four groups according to the predictors identified by multivariate analysis. The incidence rate of HCC in patients with age < 50 years and AFP < 8 ng/ml was 0.36 (95% CI = 0.06–1.19) per 100 person-years. It was lower than the pooled rate of HCC incidence rate CHB patients with Child-Turcotte-Pugh A cirrhosis demonstrated by the previous meta-analysis study (25). Although the risk of HCC development in CHB-related cirrhotic patients could not be completely eliminated by long-term NUC therapy, we found this subgroup of patients obtained more benefits from therapy with significant lower rate of HCC than other subgroup of patients. On the contrary, patients with age ≥ 50 years or/and AFP ≥ 8 ng/ml had significantly higher risk for HCC, compared with those with age < 50 years and AFP < 8 ng/ml; therefore, these patients should be closely monitored for HCC occurrence during NUC therapy.

Although male patients were determined to possessed a greater risk for HCC in previous study (19), we detected contrasting result that no significant differences in HCC risk between sexes in CHB cirrhotic patients. According to a meta-analysis performed by Zhang et al in 2019, antiviral therapy for CHB patients with TDF significantly reduced the incidence of HCC compared to those with ETV (26). However, yet other studies have reported contrasting results (27–29). As shown by Fig. 2E, our data showed similar results that the incidence of HCC in cirrhotic CHB patients didn't affect by different oral anti-viral agent (20, 27).

There was limitation of our study. The mean duration of follow-up was 47.4 ± 26.5 months in TDF-treated patients and 67.0 ± 34.8 months in ETV-treated patients, respectively. The duration was relatively shorter in the TDF group and warrant a longer follow-up period in further study to clarify the long-term effect against HCC development.

**Conclusions**

Long-term NUC therapy could not completely eliminate the risk for HCC development in CHB-related cirrhotic patients. Cirrhotic CHB patients with age < 50 years and AFP < 8 ng/ml have the lowest annual incidence of HCC, which is lower than the pooled incidence of HCC in CHB patients. However, patients with age ≥ 50 years or/and AFP ≥ 8 ng/ml have significantly higher risk for HCC and thus warrant careful surveillance schedule.

**Abbreviations**

NUC, Nucleos(t)ide analogue
HCC, hepatocellular carcinoma

CHB, chronic hepatitis B

HR, hazard ratio

CI, confidence interval

AFP, α-fetoprotein

HBV, hepatitis B virus

ETV, entecavir

TDF, tenofovir disoproxil fumarate

**Declarations**

**Ethics approval and consent to participate:** This study was approved by the Medical Ethics Committee of Chang Gung Memorial Hospital (Institutional Review Board approval number: 104_9790B)

**Consent for publication:** Not applicable

**Availability of data and materials:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests.

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**Authors' contributions:** Ching-Chih Hu, Chih-Lang Lin and Rong-Nan Chien conceived the study. Ching-Chih Hu, Pei-Hung Chang and Chih-Lang Lin contributed to data collection. Ching-Chih Hu, Man-Chin Hua and Cheng-Hao Weng analyzed the data. Ching-Chih Hu, Cheng-Hao Weng and Rong-Nan Chien contributed to writing, reviewing, and revising the paper. All authors interpreted the data and approved the final manuscript

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Figures
Figure 1

Cumulative incidence of hepatocellular carcinoma. The cumulative incidence of HCC was 0.9%, 9.8% and 22.1% at the 1, 5 and 10 years, respectively.
Figure 2

Cumulative incidence of hepatocellular carcinoma assessed by baseline risk factors: (A) age, (B) albumin, (C) HBV DNA, (D) AFP, (E) NUCs. AFP, α-fetoprotein; NUC, nucleos(t)ide analogue; TDF, tenofovir; ETV, entecavir. Patients with older age, higher AFP and HBV DNA levels, and low albumin levels have higher risk for HCC development during NUC therapy. The risk of HCC development is not different among the two NUCs.