# High percentage atypical hepatocellular carcinoma in chronic hepatitis B patients treated with nucleos(t)ide analogs

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### Abstract

Nucleos(t)ide analogs are used for preventing liver cirrhosis in chronic hepatitis B patients, but the risk factors of hepatocellular carcinoma (HCC) in these patients remain unclear. We designed this retrospective cohort study, the aim is to determine the risk factors for HCC development and its image presentation under nucleos(t)ide analogs treatment.

In this study, patients were treated with lamivudine (LAM), entecavir 0.5 mg (ETV), or telbivudine (LdT), and followed-up for at least 2 years to detect HCC and its presentation. Assessment of the risk factors for HCC included age, sex, HBeAg, viral load, liver cirrhosis, current and previous medications, and liver function tests.

Totally, 396 patients were recruited, and 18 patients developed HCC. The mean time from the treatment to HCC development was $28.5 \pm 16.7$ months. The clinical characteristics in HCC and no-HCC groups showed significant differences among age ($52.8 \pm 6.1$ vs $47.1 \pm 12.6$ years, $P < .01$), baseline alanine transaminase (ALT) levels ($161.4 \pm 177.3$ vs $361.7 \pm 496.3$, $P < .01$), and baseline liver cirrhosis (72.2% vs 29.9%, $P < .01$). In patients aged $\geq 45$ years, the hazard ratio of HCC was 10.2 and liver cirrhosis was 4.1. Majority of HCCs developed in the right liver (14/18), were single numbered (13/18), had tumor size about $1.9 \pm 0.7$ cm, were classified as T1 (14/18, TNM staging), and the atypical image occupied 88% of the HCC cases.

The patients aged $\geq 45$ years on long-term nucleos(t)ide analog therapy, and with baseline liver cirrhosis were at a high risk of HCC. Regular alpha-fetoprotein (AFP) assessment and image study of these patients are the gold standards for early HCC detection in patients with high percentage atypical HCC appearances.

**Abbreviations:** ADV = adefovir, AFP = alpha-fetoprotein, ALT = alanine transaminase, AST = aspartate transaminase, CT = computed tomography, ETV = entecavir 0.5 mg, HBV = chronic hepatitis B virus, HCC = hepatocellular carcinoma, LAM = lamivudine, LdT = telbivudine, LI-RADS = Liver Imaging Reporting and Data System, TDF = tenofovir.

**Keywords:** atypical HCC, HBV, liver cirrhosis, nucleos(t)ide analog

## 1. Introduction

Chronic hepatitis B virus (HBV) infection is an important public health problem worldwide, due to its adverse outcomes including liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). According to the Asian-Pacific HBV treatment consensus guideline-2012, lamivudine (LAM), adefovir (ADV), entecavir 0.5 mg (ETV), telbivudine (LdT), and tenofovir (TDF) can all be considered as initial therapy options for the patients with HBV infection.[1] ETV and TDF are more effective in suppressing viral levels and improving biochemical and histological characteristics of the disease, but ideal therapy duration and long-term efficacy data regarding the use of these analogs are lacking.[2] In Taiwan, half of the patients with HBV infection choose to continue antiviral drug treatment at their own expenses, while the others have to stop the treatment due to economic problems with an overall one-year clinical-relapse rate of 33.8%.[3]

Concerning the effects of the treatment with long-term nucleos(t)ide analogues on the incidence of HCC in the chronic hepatitis B patients, Wu et al reported that nucleos(t)ide analog therapy reduced the incidence of HCC in 7 years from 22.7% to 7.32% in the patients with HBV infection in Taiwan.[4] In Japan, Yasunaka et al. demonstrated that in the patients aged more than 35 years with HBV DNA level 2000 IU/mL and negative HBeAg serology, the cumulative HCC incidence in 5 years after treatment with ETV (14.6%) was equal to that in the patients not treated with an antiviral drug (13.9%) and whose alanine transaminase (ALT) level was less than 45 or the HBV DNA level was less than 2000 IU/mL.[5]

Nucleos(t)ide analog treatment may reduce the risk of HCC and overall mortality in HBV carriers, and there was a dose-response relationship between the use of nucleos(t)ide analogs and the risk

for HCC in the treated cohort.[6] Zhang et al reported that cirrhosis at baseline and failure to achieve viral response during antiviral therapy are significant risk factors for HCC development in chronic hepatitis B (CHB) patients,[7] and fibrosis-4 index can be a useful predictor of HCC development in the CHB patients undergoing ETV therapy.[8] Concerning how to detect HCC early, a study of radiological features of HCC imaging is useful not only for the diagnosis, but also for the surveillance, determining the therapy, and assessing the response to HCC treatment.[9]

In this retrospective cohort study from Mackay memorial hospital in Taiwan, we aimed to detect the risk factors and assess a possible different image presentation of HCC in the patients with HBV infection, treated with nucleos(t)ide analogs for a long-term (average 5 years) and followed-up subsequently.

## 2. Materials and methods

### 2.1. Patients and study procedure

We conducted this retrospective cohort study based on the database collected from 3 branches of Mackay Memorial

Hospital (MMH). Patients were eligible for being recruited in this study if they were ≥20 years old and had chronic HBV infection that was treated with LAM, ETV or LdT for at least 2 years. Totally, 396 consecutive patients with HBV infection, who underwent nucleos(t)ide therapy for at least 2 years from January 2009 to December 2010, were recruited. The total number of patients screened was 572, and 176 patients were excluded considering failure to follow-up during the treatment, acute liver failure during hospital stay, a treatment shift to a different nucleos(t)ide therapy in 1 year, any associated cancer in the recent 1 year, HIV infection, TB infection, age below 20 years, and an associated autoimmune disease (Fig. 1).

This study was approved by the Institutional Review Board of Mackay Memorial Hospital, Taiwan (18MMHIS042). We recruited patients from the hepatology clinics of Mackay Memorial Hospital who presented with chronic HBV infection and were treated according to the Taiwan national health insurance clinical practice guideline (HBsAg-positive and all HBeAg-negative patients with the HBV DNA level >2000 IU/mL and a serum ALT level >80 IU/L for 3 months; all the HBeAg-positive patients with the HBV DNA level >20,000 IU/mL and
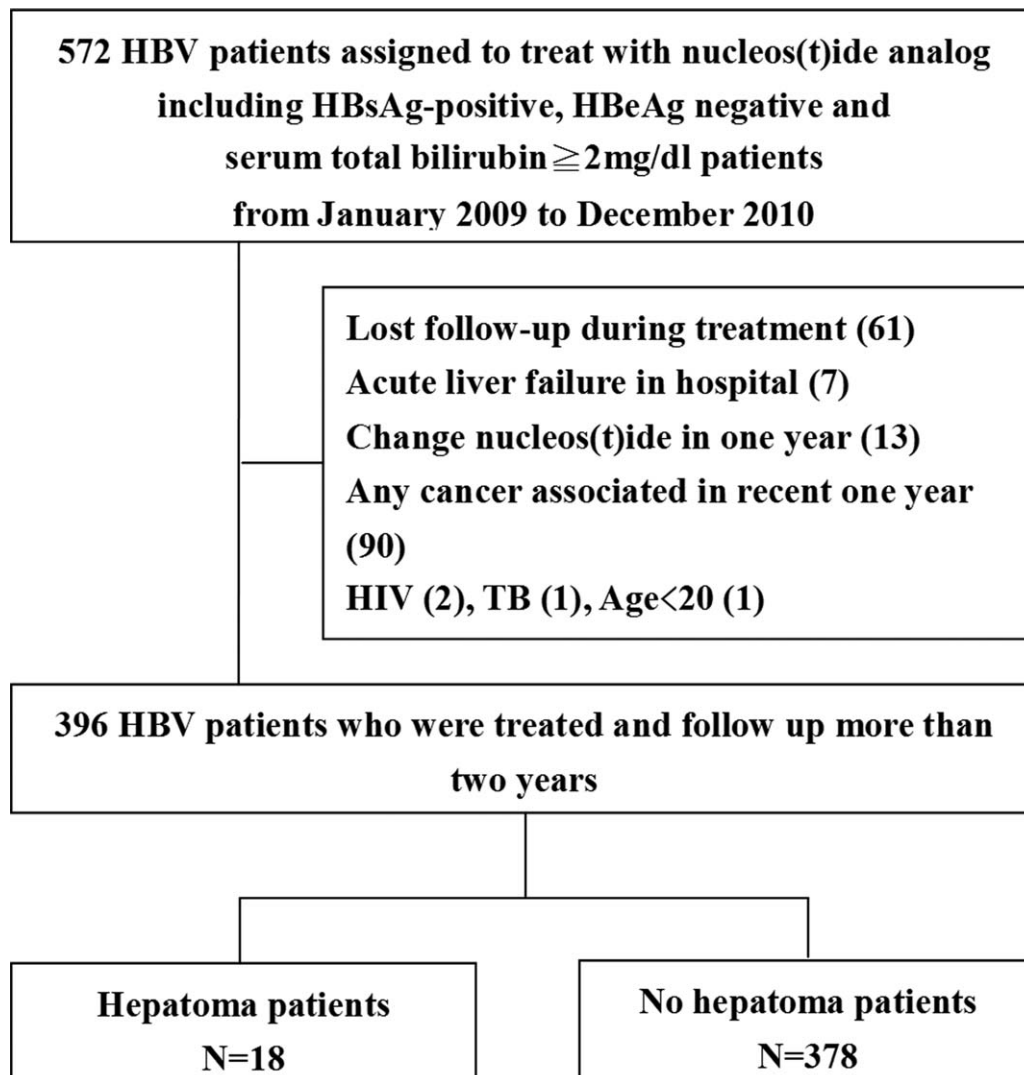


**Figure 1.** Clinical flow diagram of 572 patients with HBV enrolled for the study. Of the 396 patients treated and followed-up for more than 2 years, 18 patients developed HCC. HBV = chronic hepatitis B virus, HCC = hepatocellular carcinoma.

serum ALT level >80 IU/L; and all the patients with serum total bilirubin above or equal to 2 mg/dL).

### 2.2. Clinical data collection and follow-up

All nucleos(t)ide analog treatment recipients were followed at 1- to 3-month intervals, and biochemical and HBV virological markers were monitored. Patients underwent abdominal ultrasonography to determine the changes of cirrhosis. The HCC emergence was diagnosed and confirmed by the performing ultrasonography and helical dynamic computed tomography (CT). HCC was diagnosed by the presence of typical hypervascular characteristics on angiography, in addition to the findings of dynamic CT. If no typical findings of HCC were observed, the diagnosis was confirmed based on the Liver Imaging Reporting and Data System (LI-RADS),[10] and finally confirmed by fine needle aspiration biopsy followed by histological examination. Patients were followed until the last visit.

Age, sex, prior treatment, presence of cirrhosis, baseline biochemical data, and serum HBV viral load were recorded. Treatment was provided according to the Taiwan national health insurance clinical practice guideline, that suggests a regular follow-up by performing abdominal echo and serum HBV DNA assessments every 6 months during the treatment; and determining serum HBV DNA, aspartate transaminase (AST) (normal range, 15–41 IU/L), and ALT (normal range, 14–40 IU/L) levels every 3 to 6 months for 1 year after the 3 years of treatment. The patients were treated with additional ADV or were shifted to the treatment with ETV 1 mg for 3 years, if the viral breakthrough occurred clinically.

### 2.3. Analyses of biochemical determinants and the risk factors for HCC development

The serum ALT and AST UNL were set by the laboratory at 40 U/L and 41 U/L, respectively, for men and women; HBV DNA level was measured by a Roche Amplicor PCR assay with a lower limit of 20 IU/mL for detection and quantitation. Serum hepatitis markers including HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HCV were tested. The endpoints were the risk factors for HCC,

including age, sex, HBeAg, viral load, liver cirrhosis, current and previous medications, and liver function tests.

### 2.4. Statistical analysis

Categorical variables were compared by using the Chi-square test or Fisher exact test for each characteristic category of the patients, while continuous variables were compared with the Student $t$ test. Multivariable Cox regression model to assess the relation between age, cirrhosis and the delaying onset of HCC were constructed. Cox regression analysis was used to identify independent risk factor for delay onset HCC. The statistical analyses were performed by using a SPSS 21.0 statistical package (SPSS, Chicago, IL). Missing data were treated by using the SPSS software's missing value option. All of the statistical analyses were based on 2-sided hypothesis tests with a significance level of $P < .05$.

### 3. Results

A total of 396 chronic hepatitis B patients were recruited. The baseline patient-related and treatment-related demographics and clinical characteristics between the 2 groups, including age, sex, liver function tests, 6-month, and 12-month follow-up ALT levels, virological data, the presence of cirrhosis, treatment experience, treatment duration, and drugs for the HCC treatment were not significantly different (Table 1). The mean follow-up duration of the 2 groups was $65.8 \pm 11.8$ months and $65.5 \pm 12.5$ months, respectively. Eighteen patients developed HCC, and 15 patients (83.3%) were males. The mean age for the development of HCC was $52.8 \pm 6.1$ years.

The mean age of patients with HCC was significantly older as compared to that of patients without HCC ($52.8 \pm 6.1$ years vs $47.1 \pm 12.6$ years, $P < .001$). There was no significant difference in the baseline HBV viral load between the patients who developed HCC and those who did not ($P = .731$). The baseline ALT and AST levels of the patients with HCC were significantly lower as compared to that of patients without HCC (ALT: $161.4 \pm 177.3$ vs $361.7 \pm 496.3$, $P < .001$; AST: $124.4 \pm 93.0$ vs $245.4 \pm 385.5$, $P < .001$). The baseline prevalence rate of cirrhosis in the HCC group was higher as compared to that of no-HCC group (13/18

#### Table 1

Demographic and clinical characters of new growth hepatoma patients and no hepatoma chronic hepatitis B patients.

| | Hepatoma occurred (n = 18) | No Hepatoma patients (n = 378) | P |
|---|---|---|---|
| **Patient related** | | | |
| Male, n (%) | 15 (83.3%) | 285 (75.4%) | .580 |
| Age, mean ± SD | 52.8 ± 6.1 | 47.1 ± 12.6 | .001 |
| HBeAg(+/-) | 7/11 | 164/214 | .810 |
| Baseline ALT, mean ± SD, IU/L | 161.4 ± 177.3 | 361.7 ± 496.3 | .000 |
| Baseline AST, mean ± SD, IU/L | 124.4 ± 93.0 | 245.4 ± 385.5 | .000 |
| Baseline T. Bil, mg/dL | 3.0 ± 3.7 | 2.4 ± 2.5 | .344 |
| Baseline AFP, ng/uL | 412.6 ± 1042.6 | 26.4 ± 79.4 | .159 |
| The 6th month ALT | 37.4 ± 17.6 | 36.7 ± 33.0 | .932 |
| The 12th month ALT | 45.6 ± 30.9 | 45.8 ± 106.4 | .992 |
| Liver cirrhosis, n (%) | 13 (72.2%) | 113 (29.9%) | .000 |
| Baseline HBV Viral load $10^6$ IU/mL | 6.7 ± 130.0 | 150.0 ± 160.0 | .731 |
| **Treatment related** | | | |
| Pretreatment | 6 (33.3%) | 66 (17.5%) | .112 |
| Tx duration, M | 57.3 ± 16.5 | 51.2 ± 17.4 | .141 |
| E/L/T | 5/8/5 | 173/160/45 | .096 |
| Follow-up period, M | 65.8 ± 11.8 | 65.5 ± 12.5 | .923 |

ALT = alanine transaminase, E/L/T = entecavir/lamivudine/telbivudine, HBV = chronic hepatitis B virus, T. Bil = total bilirubin, Tx = treatment, M = months.

**Table 2**

**Hepatocellular carcinoma new growth Cox regression analysis according to patients who was treated and follow up more than 2 years.**

| Factors | Group | N | HR | (95% CI) | P value |
|---|---|---|---|---|---|
| Sex | female(R) | 96 | | | |
| | male | 300 | 2.330 | 0.669–8.114 | .184 |
| Age | age<45(R) | 169 | | | |
| | age≥45 | 227 | 10.209 | 1.338–77.909 | .025 |
| Baseline ALT | ≥200 IU/L (R) | 174 | | | |
| | < 200(IU/L) | 222 | 2.403 | 0.679–8.507 | .174 |
| Pretreatment | first treatment(R) | 324 | | | |
| | retreatment | 72 | 1.831 | 0.677–4.950 | .233 |
| Liver cirrhosis | no cirrhosis(R) | 270 | | | |
| | cirrhosis | 126 | 4.107 | 1.424–11.843 | .009 |
| NAs | LAM or LdT(R) | 219 | | | |
| | ETV | 177 | 0.712 | 0.248–2.043 | .528 |

HR = hazard ratio, N = patient number, NAs = nucleos(t)ide analoges, R = reference.

(72.2%) vs 113/378 (29.9%), $P$<.001). On the contrary, the baseline total bilirubin and alpha-fetoprotein (AFP) levels in both the groups did not show significant differences. In addition, the 6-month and 12-month ALT levels after the treatment initiation in the HCC group and the no-HCC group were not significantly different. We used cox regression analysis to identify the risk factors in terms of sex, age, baseline ALT levels, pre-treatment experience, nucleos(t)ide analogs and the presence of liver cirrhosis; the results showed only age (HR: 10.2; $P$=.025) and the presence of liver cirrhosis (HR: 4.1; $P$=.009) as independent factors, which contributed to the incidence of HCC (Table 2).

The HCC characteristics, distribution, size, and staging in the 18 patients who developed HCC within 3 years after the initiation of the nucleos(t)ide treatment. The gender, age, and the presence of liver cirrhosis are described as above. Five patients were found suffering HCC after the first year antivirus treatment, 4 patients developed HCC in the second year, and 9 patients developed after 2 years. The average time for HCC development in the 18 patients was 28.5 ± 16.7 months, and the cumulative incidence of HCC based on the age, the presence of liver cirrhosis and the effect of different nucleos(t)ide analogs is showed in

Figure 2. Thirteen patients who developed HCC had only 1 tumor, 2 patients had 2 tumors, 1 patient had 3 tumors, and 2 patients developed multiple tumors. Regarding tumor size, the average size of the tumor was 1.9 ± 0.7 cm. According to TNM system, 13 patients with HCC presented with the tumor size of T1 stage, 4 patients with the tumor size of T2 stage, and 1 with the tumor size of T4 stage on detection. Regarding tumor distribution, only 4 patients developed the HCC in the left liver, while the other 14 patients developed the tumor in the right liver (Table 3). Atypical HCC images, according to the LI-RADS including LR3 and LR4, were observed in about 13/15 (88%) patients as shown in Figure 3.

## 4. Discussion

There are more than 200 million people living with HBV infection, but only 10% have been diagnosed and less than 1% has been treated adequately. The barriers to diagnosis and treatment include lack of knowledge about HBV-related diseases, insufficient screening and referral to care, limited treatment due to limited drug availability, medical reimbursement policies, and
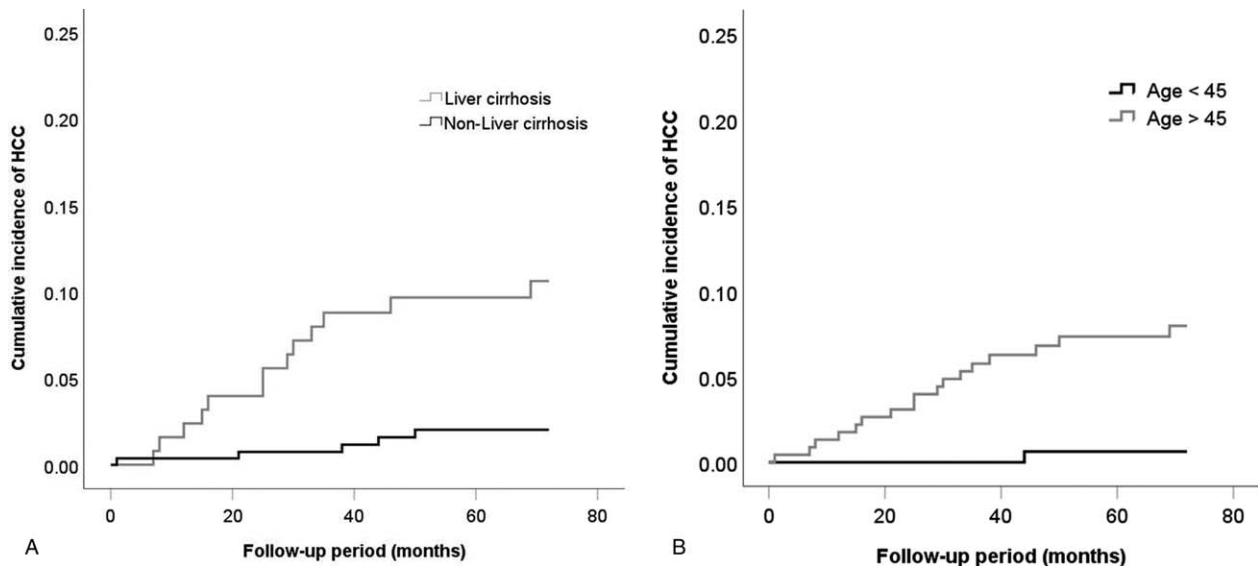


**Figure 2.** The cumulative incidence of HCC according to the age, the presence of liver cirrhosis by Kaplan–Meier method. HCC = hepatocellular carcinoma.

**Table 3**

**Baseline hepatoma characteristics, tumor distribution, size, and staging.**

| Case No. | Sex | Age | L C | Time to HCC (m) | Tumor Number | Tumor Location | Tumor size cm | TMN | LI-RADS |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 49 | + | 8 | 1 | R | 1.5 | T1 | LR3 |
| 2 | M | 44 | − | 44 | 1 | R | 1.8 | T1 | LR4 |
| 3 | M | 53 | − | 50 | 1 | R | 1.9 | T1 | NC |
| 4 | M | 45 | + | 46 | 1 | R | 2.5 | T1 | LR4 |
| 5 | M | 52 | + | 69 | 2 | R | 1.8 | T2 | LR4 |
| 6 | M | 52 | + | 7 | 1 | L | 2.4 | T1 | LR4 |
| 7 | M | 54 | + | 12 | 2 | R | 1.7 | T2 | LR3 |
| 8 | M | 60 | − | 21 | 1 | L | 2.1 | T1 | LR4 |
| 9 | M | 55 | + | 25 | 1 | R | 1.8 | T1 | LR3 |
| 10 | M | 54 | + | 29 | 1 | L | 1.3 | T1 | LR4 |
| 11 | F | 70 | − | 1 | 1 | R | 3.2 | T1 | LR5* |
| 12 | M | 52 | + | 16 | 1 | R | 1.5 | T1 | LR3 |
| 13 | M | 56 | + | 15 | 3 | R | 1.0 | T2 | LR3 |
| 14 | M | 51 | + | 30 | 1 | R | 2.2 | T1 | LR4 |
| 15 | M | 48 | − | 38 | M | R | 1.0 | T4 | NC |
| 16 | F | 58 | + | 35 | 1 | R | 1.6 | T1 | LR4 |
| 17 | M | 46 | + | 25 | 1 | L | 3.6 | T1 | LR5 |
| 18 | F | 51 | + | 33 | M | R | 1.5 | T2 | NC |

L = left liver, LC = liver cirrhosis, LI-RADS = Liver Imaging Reporting and Data System, m = months, NC = Non Categorizable, R = right liver.

* There was the other 1 tumor about 12 mm (LR3) in case 11 which image showed no change through 2 years observation.
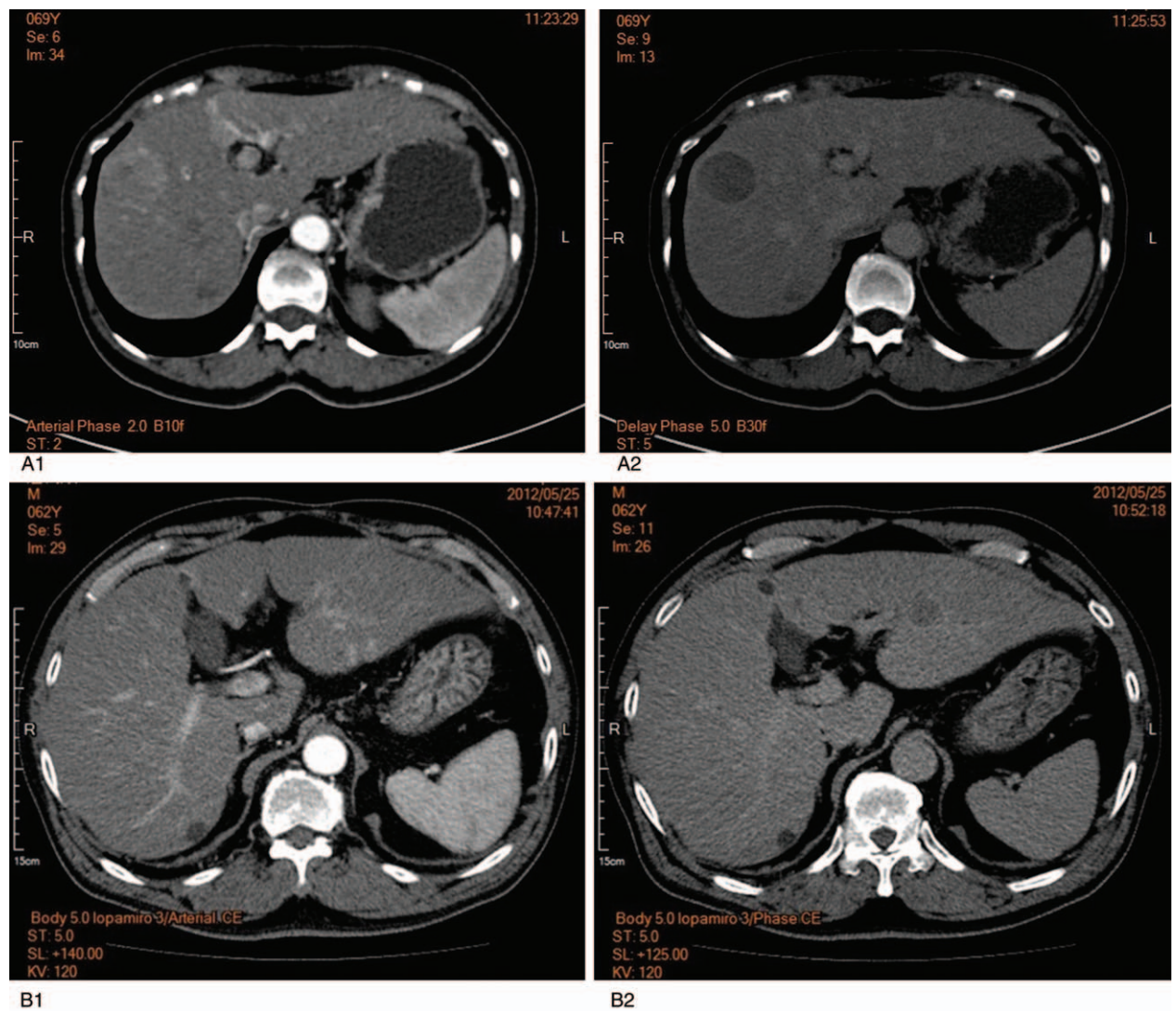


**Figure 3.** Atypical HCC images including LR3, LR4 and LR5. 3a. LR3: Intermediate probability of Malignancy in case 11. A 2.7x3.2 cm early enhancing mass (LR5) at S8 of liver appeared contrast washout on portal & delayed phases, suggestive of hepatoma, but an all phases hypodense focal lesion about 1.2cm(LR3) at S7 of liver suspected dysplastic nodule or atypical hepatoma. 3b. LR4: Probably HCC in case 8. A 2.1 cm hypodense hepatic nodule (LR4) in S2/3 segment is visible in portovenous and delayed phase which suspect an atypical hepatoma or dysplastic nodule. HCC = hepatocellular carcinoma.

the need for long-term or life-long therapy.[11] Oral nucleos(t)ide analogs have good antiviral effect during the treatment period but tend to have poor durability after therapy discontinuation. Oral nucleos(t)ide analog treatment in chronic hepatitis B may decrease the number of annual deaths by 62.3%, which may increase the life expectancy. In contrast, the number of annual deaths due to liver cancer has increased by 17.8%. The competing changes between the situations of deaths from liver disease and liver cancer should be carefully considered in setting a health care policy.[12] In the real world data of Taiwan in 2007, Chen reported that the cumulative incidence of HCC was 10% after 9 years of follow-up of the hepatitis B e-antigen positive carriers.[13] In our study, we found that of 396 chronic hepatitis B patients, most of the patients treated with oral nucleos(t)ide analogs for 3 years and followed-up for more than 5 years (18 patients, 4.5%) developed HCC.

Some demographic and clinical characters might be correlated with HCC occurrence during oral nucleos(t)ide analog treatments of the chronic hepatitis B patients. In one 7-year cohort study of the chronic hepatitis B patients receiving ETV treatment, 34 patients (total 804) developed HCC, and 88% of these HCC patients presented with liver cirrhosis before treatment initiation.[14] Watanabel reported that the annual incidence of HCC decreased after starting the ETV treatment over the time after 3 years. On multivariate analysis of HCC incidence, older age and low platelet count were observed as significant, independent contributing factors.[15] Bi et al reported that long-term (>6 months, except for LAM monotherapy) nucleos(t)ide analogs therapy can delay the onset of HCC in patients with HBV-related cirrhosis.[16] In this study, we found that age, presence of liver cirrhosis are independent factors correlated with the HCC occurrence in the chronic hepatitis B patients treated with oral nucleos(t)ide analogs.

Some factors are associated with chronic HBV disease progression, including age, sex, HBV genotype, HBV DNA serum viral load, treatment duration, and presence of HBeAg, but which factors are correlated with the HCC occurrence remain unknown. The risk for HCC is higher in the cirrhotic patients than that in the non-cirrhotic patients, and some people use a scoring system for the HCC prediction.[17] In 1 recent study, Tseng et al. reported that non-cirrhotic patients with the chronic HBV infection, Fibrtosis-4 index <1.29 complements the existing clinical profile which may define the patients with the lowest risk for HCC.[18] In this study, we found that the hazard ratio for the age more than 45 years was 10.2 and the hazard ratio for the liver cirrhosis was 4.1.

Chen et al reported a prospective cohort (3653 participants, aged 30–65 years) chronic hepatitis B community-based cancer screening program in Taiwan between 1991 and 1992, the cumulative incidence rates of HCC were 1.3% (HBV DNA level less than 300 copies/mL) and 14.9% (HBV DNA level 1 million copies/mL or greater) respectively, and elevated serum HBV DNA level (> or =10,000 copies/mL) is a strong risk predictor of HCC.[19] In Taiwan, 1 retrospective multiple center study showed 4-year ETV therapy significantly reduces the risk for HCC, cirrhotic events, and mortality in the chronic hepatitis B patients.[20] Among cirrhotic patients, the incidence of HCC can be reduced in those with HBV infection treated consecutively with LAM or in those with HBV DNA levels <2000 IU/mL. According to a previous literature, the risk factors correlated to HCC development in the chronic hepatitis patients include age more than 50 years, platelet count less than $14.0 \times 10^4/mm^3$, and hepatitis B e-antigen negativity.[21] In our study, we found that the cumulative HCC incidence significantly increased during the first 3 years of the follow-up period for the chronic hepatitis B in the patients aged more than 45 years and in those with liver cirrhosis (Fig. 2), that is, early treatment of the chronic hepatitis B with oral nucleos(t)ide analogs is important to prevent the development of liver cirrhosis and HCC. Although ETV had more effects in suppressing viral levels and improving biochemical and histological disease features than LAM and LdT, but not in HCC new growth Cox regression analysis during the long-term follow-up (HR 0.71, $P = .528$).

In clinical practice, regular (3–6 months) abdominal sonography examination and serum AFP estimation in the chronic hepatitis B patients with or without liver cirrhosis are the gold standard methods to screen HCC; and liver CT angiography or liver MRI may be the next step if an increased AFP serum level is obtained, or space-occupying lesion is detected on abdominal sonography. HCC image is usually presented with typical characteristics, but may sometimes present with a wide spectrum of atypical appearances. Although these atypical appearances are uncommon, the associated doctors may need to be familiar with the unusual presentations; and their imaging findings are critical to ensure accurate diagnosis and treatment.[22] For this reason, the LI-RADS are used for different patient populations for surveillance and for diagnosis and staging.[23] This classification is a comprehensive system for standardizing the acquisition, interpretation, reporting, and data collection of liver imaging, such as LR3 for intermediate probability of malignancy, LR4 for probably HCC, and LR5 for definite HCC. According to previous literature, Choi et al reported that a total 216 patients (77% had HBV infection) who underwent surgery with 304 pathologically proved HCC; the atypical enhancement pattern (MR images) was about 28.3%.[24] In this study, we found that the majority of the tumors showed presented as a single, small-sized, and atypical image (6 cases: LR3, and 8 cases: LR4), which might interfere with the correct diagnosis and the treatment recommendation by the doctors. Close observation for about 6 months to find the threshold growth is important, and the alternative method is to perform contrast sonography examination. Our study had numerous limitations. First, it was a retrospective cohort study and included only a small sample of the patients treated for HBV infection. Second, tests for HBV genotype and mutation are not currently available within the Taiwanese national health insurance budget.

In conclusion, this study showed that patients with chronic HBV infection in Taiwan, whether HBeAg(+) or HBeAg(-), who were treated and followed-up for more than 2 years presented with a 4.5% occurrence rate of HCC; and the patients aged more than 45 years on long-term nucleos(t)ide analog therapy or having liver cirrhosis may have the risk of developing HCC. High percentage atypical HCC image obtained by CT scanning may disturb the clinical doctors in the decision making about the diagnosis and the treatment of HCC.

## Author contributions

**Conceptualization:** Ching Chung Lin, Ming-Jong Bair, Tsang-En Wang.

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