Comparison of nucleoside and nucleotide analogs in the recurrence of hepatitis B virus-related hepatocellular carcinoma after surgical resection: A multicenter study

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Abstract
Background: Antiviral therapy should reduce the recurrence of hepatitis B virus-related hepatocellular carcinoma (HBV-related HCC) after surgical resection. However, there is little research on whether various antiviral drugs have different prognostic effects in patients with HBV-related HCC after curative liver resection. The present study compared the effects of nucleotide analog (NtA) and nucleoside analog (NsA) antiviral therapies after surgical resection on the prognosis of HBV-related HCC.

Methods: A total of 1303 patients with HBV-related HCC who received curative hepatectomy at five institutes between April 2014 and April 2019 were retrospectively enrolled and analyzed. Propensity matching analysis was used to compare the outcomes of HCC patients given NsA versus NtA therapy. Subgroup analysis was performed to compare the outcomes of patients treated with entecavir (ETV) and tenofovir disoproxil fumarate (TDF) antiviral therapies after surgical resection on the prognosis of HBV-related HCC.

Results: Among 1303 patients, 759 (58.2%) patients developed recurrence, and 460 (35.3%) patients died. Multivariable analyses revealed that NtA therapy significantly decreased the risk of HCC recurrence (hazard ratio [HR], 0.64; 95% confidence interval [CI], 0.51–0.80; p < 0.001) and HCC-related death (HR, 0.52; 95% CI, 0.36–0.76; p = 0.001) compared to NsA therapy. Subgroup analysis showed that TDF treatment was associated with significantly lower rates of HCC recurrence (HR, 0.64; 95% CI, 0.49–0.83; p = 0.001) and death (HR, 0.32; 95% CI, 0.20–0.50; p < 0.001) than ETV treatment.

Conclusions: Nucleotide analog treatment, but not NsA treatment, significantly reduced the risk of HCC recurrence in patients with HBV-related HCC and improved overall survival after curative hepatic resection.

Keywords
hepatitis B virus, hepatocellular carcinoma, nucleos(t)ide analogs, recurrence, resection
1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most frequently diagnosed cancer and the third most frequent cause of death worldwide. HCC is the fourth most common malignant tumor in China and the second leading cause of death, largely because hepatitis B virus (HBV) infection, which is the major cause of HCC development, is epidemic in China. Hepatocotomy is the mainstay of HCC treatment, and it leads to expected outcomes (5-year survival of 60%–80%) in well-selected candidates. However, a high recurrence rate of approximately 60% after curative hepatic resection at 5 years is the main factor affecting the prognosis of HCC. High serum levels of HBV-DNA are an important predictor of HCC recurrence. Previous well-designed studies demonstrated that antiviral therapy reduced the risk of postoperative recurrence of HBV-related HCC.

Recently, Choi et al. found that patients treated with tenofovir disoproxil fumarate (TDF) had a lower risk of postoperative HCC recurrence than those treated with entecavir (ETV), but Lee et al. found no significant difference in the risk of recurrence and death between the ETV and TDF groups. Currently, direct-acting antivirals include nucleotide analogs (NtAs) and nucleoside analogs (NsAs). The commonly used nucleoside analogs (NUCs) that act as direct-acting antivirals include but are not limited to TDF and ETV. Additionally, the potential impact of direct-acting antivirals on HCC recurrence is still a controversial topic. It is still unclear whether NtAs and NsAs have different effects on HCC recurrence rates in patients with HBV-related HCC after curative resection.

Therefore, we aimed to compare the different effects of NtAs and NsAs on HCC recurrence and overall survival (OS) in patients with HBV-related HCC after curative resection.

2 | MATERIALS AND METHODS

2.1 | Study population

Using a retrospectively collected database, we identified patients with HBV-associated HCC who underwent therapeutic liver resection in five participating institutions between April 2014 and April 2019 (Figure 1). The participating institutions included The Affiliated Cancer Hospital of Guizhou Medical University, the Affiliated Hospital of Chengdu University, the People’s Hospital of Leshan, Sichuan Provincial People’s Hospital, and West China Hospital of Sichuan University. HBV-related HCC was defined as progression to HCC after the detection of serum hepatitis B surface antigen (HBsAg) for at least 6 months. The patients were divided into NsA and NtA groups.

We excluded patients who satisfied any of the following criteria: (1) other concurrent malignancies or recurrent HCC; (2) coinfection with other viruses (e.g., hepatitis C virus, hepatitis D virus, or human immunodeficiency virus); (3) preoperative antitumor treatment; (4) use of other antiviral therapies, such as interferon; (5) treatment with a combination of NUCs; (6) no/irregular treatment with NUCs; and (7) poor liver function (Child-Turcotte-Pugh [CTP] class C, Figure 1).

Baseline patient and tumor characteristics were obtained from electronic medical records at each medical center and included patient demographics, HBsAg, hepatitis B virus e antigen, serum HBV-DNA load, alpha fetoprotein (AFP), coagulation function, liver function, renal function, and hematological parameters. Hepatic pathologists assessed tumor characteristics in the excised specimens. The antiviral choice for each patient was based on their socio-economic status and the preferences of each doctor.

This study was performed according to the World Medical Association Declaration of Helsinki and approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University (IRB No. 2021-311).

2.2 | Follow-up

All patients were followed up at 1 month postoperatively, every 3 months for the first 3 years and every 6 months for the next few years. The tumor evaluation and follow-up protocol included multiphasic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), physical examination, blood cell and differential counts, liver function tests, AFP levels, HBV markers, and HBV-DNA levels.

The primary endpoint was recurrence-free survival (RFS), and the secondary endpoint was OS. The index date was defined as the date of hepatectomy for HCC. RFS was defined as the interval between surgery and the first incidence of positive recurrence. OS was defined as the time interval between surgery and death of any cause or last follow-up. The last date of follow-up was 31 March 2021.

Tumor recurrence was defined as multiphasic contrast-enhanced CT or MRI showing intrahepatic lesions with typical HCC enhancement characteristics, that is, contrast enhancement in the arterial phase and washout in the venous phase.

2.3 | Statistical analysis

To balance the baseline characteristics and minimize the effect of potential confounders, nearest-neighbor 1:2 propensity score matching (PSM) with a caliper size of 0.02 was used to reduce group differences in covariances between NsA and NtA patients (Figure 1). Propensity scores were calculated using the following 20 variables: age, sex, Barcelona Clinic
Liver Cancer (BCLC) stage, tumor size, tumor number, microvascular invasion (MVI), diabetes, hypertension, serum HBV-DNA level, HBsAg, AFP, prothrombin time (PT), red blood cell count, hemoglobin, white blood cell count, platelets, aspartate aminotransferase (AST), alanine aminotransferase, albumin (ALB), and total bilirubin.

Baseline characteristics were grouped into continuous and categorical variables. Continuous variables, which are reported as the means ± standard deviation, were compared between groups using the t-test or the Mann–Whitney U test. Categorical variables were compared using the χ² test or Fisher’s exact test, and the results are expressed as numbers (n) or proportions (%). Cumulative RFS and OS rates were analyzed using the Kaplan–Meier method, and differences were compared using the logarithmic rank test. Univariable and multivariable Cox proportional risk regression analyses were performed to identify predictors associated with RFS and OS and assess risk factors that lead to recurrence and death.

All statistical analyses were performed using R statistical software version 4.0.4 (R Foundation for Statistical Computing) and SPSS software version 25.0 (SPSS). A two-tailed p value < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

The study included 1303 patients: 1105 (84.8%) received NsA postoperatively; and 198 (15.2%) received NtA postoperatively. Table 1 shows the patient characteristics for
| Characteristics          | Entire cohort (n = 1303) | Propensity score-matched cohort A (198 pairs, n = 594) | Propensity score-matched cohort B (144 pairs, n = 432) |
|-------------------------|-------------------------|------------------------------------------------------|------------------------------------------------------|
|                         | NsA (n = 1105)          | NtA (n = 198)                                        | ETV (n = 288)                                        | TDF (n = 144) |
| Age, years              | 51.4 ± 11.1             | 50.4 ± 11.6                                         | 50.4 ± 10.3                                         | 49.3 ± 10.6  |
|                         |                         | 0.265                                                | 0.985                                                | 0.610        |
| Male sex, n (%)         | 936 (84.7)              | 165 (83.3)                                          | 323 (81.5)                                          | 247 (85.7)   |
|                         |                         | 0.623                                                | 0.596                                                | 0.772        |
| Hypertension, n (%)     | 312 (28.2)              | 45 (22.7)                                           | 99 (25.0)                                           | 57 (19.7)    |
|                         |                         | 0.110                                                | 0.542                                                | 0.932        |
| Diabetes mellitus, n (%)| 138 (12.4)              | 25 (12.6)                                           | 44 (11.1)                                           | 43 (14.9)    |
|                         |                         | 0.957                                                | 0.587                                                | 0.772        |
| BMI, kg/m²              | 23.1 ± 3.1              | 23.2 ± 3.0                                          | 23.1 ± 3.1                                          | 23.1 ± 3.1   |
|                         |                         | 0.630                                                | 0.895                                                | 0.301        |
| HBeAg positive, n (%)   | 248 (22.4)              | 42 (21.2)                                           | 90 (22.7)                                           | 56 (23.0)    |
|                         |                         | 0.701                                                | 0.675                                                | 0.806        |
| HBV DNA, IU/ml          | 1.05 ± 4.42 x 10⁶       | 7.40 ± 3.98 x 10⁶                                   | 7.24 ± 3.57 x 10⁶                                   | 7.40 ± 3.98 x 10⁶ |
|                         |                         | 0.420                                                | 0.966                                                | 0.988        |
|                         |                         |                                                      |                                                      |              |
| HBV DNA > 10³ IU/ml, n (%)| 670 (60.6)         | 91 (45.9)                                            | 189 (47.7)                                          | 157 (54.5)   |
|                         |                         | <0.001                                              | 0.684                                                | 0.733        |
| AFP, ng/ml              | 2983.58 ± 19277.00      | 1127.69 ± 7039.56                                   | 1899.08 ± 11221.32                                  | 2331.38 ± 17205.12 |
|                         |                         | 0.034                                                | 0.432                                                | 0.443        |
|                         |                         |                                                      |                                                      |              |
|                         |                         |                                                      |                                                      |              |
|                         |                         |                                                      |                                                      |              |
| Total bilirubin, mg/dl  | 16.28 ± 17.48           | 14.35 ± 5.73                                        | 14.35 ± 6.19                                        | 14.48 ± 6.90 |
|                         |                         | 0.124                                                | 0.991                                                | 0.834        |
| Albumin, g/L            | 42.29 ± 5.07            | 43.18 ± 4.65                                        | 43.33 ± 5.52                                        | 43.18 ± 5.28 |
|                         |                         | 0.022                                                | 0.750                                                | 0.675        |
| ALT, IU/ml              | 50.47 ± 56.41           | 46.41 ± 34.93                                       | 44.60 ± 38.12                                       | 49.50 ± 49.35 |
|                         |                         | 0.327                                                | 0.575                                                | 0.843        |
| AST, IU/ml              | 53.71 ± 53.41           | 43.45 ± 38.14                                       | 41.43 ± 23.46                                       | 46.25 ± 36.11 |
|                         |                         | <0.001                                              | 0.379                                                | 0.632        |
| PT, s                   | 12.6 ± 3.1              | 12.3 ± 1.0                                          | 12.3 ± 2.4                                          | 12.1 ± 0.9   |
|                         |                         | 0.025                                                | 0.775                                                | 0.521        |
| RBC, ×1000/mm³          | 4.72 ± 0.67             | 4.68 ± 0.61                                         | 4.68 ± 0.61                                         | 4.70 ± 0.61  |
|                         |                         | 0.352                                                | 0.946                                                | 0.994        |
| WBC, ×1000/mm³          | 6.85 ± 22.34            | 5.28 ± 2.12                                         | 5.17 ± 1.74                                         | 5.47 ± 1.99  |
|                         |                         | 0.321                                                | 0.524                                                | 0.585        |
| PLT, ×1000/mm³          | 146.6 ± 74.7            | 137.9 ± 70.1                                        | 137.7 ± 68.9                                        | 142.6 ± 68.2 |
|                         |                         | 0.126                                                | 0.973                                                | 0.754        |
| Hemoglobin, g/L         | 143.4 ± 19.0            | 142.8 ± 18.8                                        | 143.8 ± 18.8                                        | 143.4 ± 19.9 |
|                         |                         | 0.707                                                | 0.547                                                | 0.850        |
| BCLC stage              |                         |                                                      |                                                      |              |
| Very early (0)          | 60 (5.4)                | 22 (11.1)                                           | 33 (8.3)                                            | 18 (6.2)     |
|                         |                         |                                                      |                                                      | 10 (6.9)     |
| Early (A)               | 824 (74.5)              | 148 (74.7)                                          | 300 (75.7)                                          | 212 (73.6)   |
|                         |                         | 0.003                                                | 0.332                                                | 0.702        |
| Intermediate (B)        | 67 (6.0)                | 9 (4.5)                                              | 28 (7.0)                                            | 19 (6.5)     |
|                         |                         |                                                      |                                                      | 8 (5.5)      |
| Advanced (C)            | 154 (13.9)              | 19 (9.5)                                             | 35 (8.8)                                            | 39 (13.5)    |
|                         |                         |                                                      |                                                      | 19 (13.1)    |
| Single tumor, n (%)     | 1001 (90.5)             | 178 (89.8)                                          | 352 (88.8)                                          | 253 (87.8)   |
|                         |                         | 0.761                                                | 0.708                                                | 0.752        |

(Continues)
the entire cohort. The median age was 51.2 years, and 1101 (84.4%) patients were male. The patients in NsA group had lower levels of ALB \( (p = 0.022) \), higher levels of AFP \( (p = 0.034) \), higher levels of AST \( (p < 0.001) \), longer PT \( (p = 0.0025) \), and larger tumor size \( (p < 0.001) \) compared with NtA group. More patients in the NsA group had higher serum HBV-DNA levels \( (>1000 \text{ IU/ml}; p < 0.001) \) and later BCLC stage \( \text{BCLC stage B and C; } p = 0.003 \).

Propensity score matching adjustment resulted in 594 patients, and none of the parameters of the two groups continued to be significantly different (Table 1). The characteristics between patients treated with ETV and TDF were not significantly different (Table 1).

### 3.2 | Difference in RFS based on NsA or NtA therapy

With a median follow-up time of 47.0 months for the 1303 patients, 759 (58.2%) patients developed recurrence. RFS in NtA group was significantly longer than in NsA group (hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.49–0.75; \( p < 0.001 \); Figure 2A). The cumulative recurrence rates were 36.1%, 56.5%, and 65.5% at 1, 3, and 5 years, respectively (Figure 2A).

Of the 567 PSM patients (396 in the NsA group and 198 in the NtA group), 228 (57.5%) patients in the NsA therapy group developed recurrence, and 90 (45.4%) patients in the NtA therapy group developed recurrence. There was a significant difference in RFS between patients who received NsA and NtA therapy, and the NtA group had a better RFS rate (HR, 0.67; 95% CI, 0.52–0.85; \( p = 0.001 \); Figure 3A). The 1-, 3-, and 5-year recurrence rates in the NsA treatment group were 34.8%, 55.9%, and 65.1%, respectively, and 19.9%, 42.4%, and 52.4%, respectively, in the NtA treatment group (\( p = 0.001 \), Figure 3A).

Multivariate Cox regression analyses of 1303 patients were performed to determine RFS predictors of recurrence in patients with HBV-related HCC after hepatectomy, and parameters significantly associated with recurrence risk in univariate analysis were incorporated into multivariate analysis. The multivariate Cox regression model included the entire cohort of 1303 patients. NtA treatment was associated with a significantly lower risk of HCC recurrence than NsA treatment (HR, 0.64; 95% CI, 0.51–0.80; \( p < 0.001 \); Table 2), independent of other predictive factors. Independent risk factors for HCC recurrence included younger age (HR, 1.22; 95% CI, 1.02–1.48; \( p = 0.03 \)), later stage of BCLC (HR, 1.30; 95% CI, 1.06–1.61, \( p = 0.01 \)), larger tumor size (HR, 1.78; 95% CI, 1.51–2.08, \( p < 0.001 \)), multiple tumors (HR, 1.33; 95% CI, 1.03–1.73; \( p = 0.03 \)), cirrhosis (HR, 1.52; 95% CI, 1.20–1.92; \( p < 0.001 \)), MVI (HR, 1.52; 95% CI, 1.28–1.80; \( p < 0.001 \)).

| Characteristics | Entire cohort \((n = 1303)\) | Propensity score-matched cohort A \((n = 396)\) | Propensity score-matched cohort B \((n = 432)\) | \( p \) \| Value |
|-----------------|--------------------------------|---------------------------------|---------------------------------|-------|
| **Tumor size, cm** | 6.5 ± 4.1 | 5.2 ± 3.6 | 5.2 ± 3.6 | <0.001 |
| **Cirrhosis, n (%)** | 932 (84.3) | 173 (87.3) | 0.274 | 173 (87.3) | 0.274 | 0.274 |
| **MVI, n (%)** | 294 (26.6) | 49 (24.7) | 0.584 | 49 (24.7) | 0.584 | 0.584 |
| **Capsular invasion, n (%)** | 500 (45.2) | 15 (7.5) | 0.331 | 15 (7.5) | 0.331 | 0.331 |
| **Satellite nodules, n (%)** | 136 (12.3) | 94 (47.4) | 497 (44.9) | 0.055 | 497 (44.9) | 0.055 | 0.055 |
| **Tumor differentiation** | Low 497 (44.9) | 94 (47.4) | 519 (56.0) | 0.501 | 519 (56.0) | 0.501 | 0.501 |
| **Intermediate** | 14 (1.2) | 102 (51.5) | 476 (53.9) | 209 (52.7) | 209 (52.7) | 209 (52.7) | 209 (52.7) |
| **High** | 14 (1.2) | 102 (51.5) | 476 (53.9) | 209 (52.7) | 209 (52.7) | 209 (52.7) | 209 (52.7) |

**TABLE 1** (Continued)
capsular invasion (HR, 1.18; 95% CI, 1.02–1.37; \( p = 0.03 \)),
presence of satellite nodules (HR, 1.30; 95% CI, 1.05–1.60;
\( p = 0.02 \)), lower preoperative ALB level (HR, 1.22; 95% CI,
1.04–1.43; \( p = 0.02 \)), and higher preoperative AST level
(HR, 1.48; 95% CI, 1.15–1.90; \( p = 0.002 \); Table 2).

### 3.3 Difference in OS based on NsA or NtA therapy

Among the 1303 patients, 460 (35.3%) patients died
during the follow-up period. OS in NtA group was sig-
ificantly longer than in NsA group (HR, 0.38; 95% CI, 0.27–0.54;
\( p < 0.001 \); Figure 2B). The OS rates at 1, 3,
and 5 years were 15.9%, 33.0%, and 41.2%, respectively
(Figure 2B).

For the 594 PSM patients, 119 (30%) patients in the NsA
group died, and 34 (17.1%) patients in the NtA group died.
The NtA group had significantly better OS than the NsA
group (HR, 0.52; 95% CI, 0.36–0.76; \( p = 0.001 \); Figure 3B),
and the 1-, 3-, and 5-year OS rates were 85.4%, 72.0%, and
64.2%, respectively, with NsA therapy and 93.4%, 83.5%,
and 80.0%, respectively, with NtA therapy (\( p = 0.001 \),
Figure 3B).

Multivariable Cox regression analyses including 1303
patients revealed that NtA treatment was independent of
other predictive factors, and the risk of death was signifi-
cantly lower than NsA treatment (HR, 0.41; 95% CI, 0.29–
0.59; \( p < 0.001 \); Table 2). Independent risk factors for death
included later stage of BCLC (HR, 2.06; 95% CI, 1.61–2.62;
\( p < 0.001 \)), larger tumor size (HR, 1.87; 95% CI, 1.51–
2.33; \( p < 0.001 \)), cirrhosis (HR, 1.70; 95% CI, 1.22–2.37;
\( p = 0.002 \)), MVI (HR, 1.48; 95% CI, 1.20–1.82; \( p < 0.001 \)),
presence of satellite nodules (HR, 1.41; 95% CI, 1.10–1.81;
\( p = 0.01 \)), poor tumor differentiation (HR, 1.26; 95% CI,
1.04–1.52; \( p = 0.02 \)), higher preoperative HBV-DNA load
(HR, 1.28; 95% CI, 1.04–1.58; \( p = 0.02 \)), higher preoper-
ative AFP level (HR, 1.46; 95% CI, 1.21–1.77; \( p < 0.001 \)),
lower preoperative ALB level (HR, 1.40; 95% CI, 1.15–1.70;
\( p = 0.001 \)), and higher preoperative AST level (HR, 1.34;
95% CI, 1.00–1.78; \( p = 0.048 \); Table 2).

### 3.4 Subgroup analysis of TDF versus ETV

Entecavir versus TDF subgroup analysis included 432
patients (288 ETV and 144 TDF). A total of 162 (56.2%)
patients in the ETV therapy group developed recurrence, and 65 (45.1%) patients in the TDF therapy group developed recurrence. The TDF group showed a significantly better RFS (HR, 0.70; 95% CI, 0.53–0.93; \( p = 0.015 \); Figure 4A). The 1-, 3-, and 5-year recurrence rates were 37.1%, 54.3%, and 67.9%, respectively, with ETV therapy and 21.8%, 44.3%, and 53.6%, respectively, with TDF therapy (\( p = 0.013 \), Figure 4A).

Among these patients, 101 (35.0%) patients in the ETV group and 20 (13.8%) patients in the TDF group died. The TDF group exhibited significantly lower mortality (HR, 0.35; 95% CI, 0.22–0.57; \( p < 0.001 \), Figure 4B). ETV therapy resulted in 1-, 3-, and 5-year OS rates of 81.7%, 66.3%, and 59.9%, respectively, and TDF therapy resulted in OS rates of 94.4%, 86.3%, and 84.8%, respectively (\( p < 0.001 \), Figure 4B).

The multivariable Cox regression model revealed that the TDF group showed significantly better RFS (HR, 0.64; 95% CI, 0.49–0.83; \( p = 0.001 \)) and OS (HR, 0.32; 95% CI, 0.20–0.50; \( p < 0.001 \)) than the ETV group, and TDF was an independent protective factor for HCC recurrence and death (Table 3). Independent risk factors for HCC recurrence included younger age (HR, 1.22; 95% CI, 1.01–1.48; \( p = 0.04 \)), later stage of BCLC (HR, 1.32; 95% CI, 1.06–1.65; \( p = 0.02 \)), larger tumor size (HR, 1.78; 95% CI, 1.50–2.10, \( p < 0.001 \)), cirrhosis (HR, 1.50; 95% CI, 1.19–1.90; \( p = 0.001 \)), MVI (HR, 1.52; 95% CI, 1.27–1.82; \( p < 0.001 \)), capsular invasion (HR, 1.20; 95% CI, 1.02–1.40; \( p = 0.03 \)), presence of satellite nodules (HR, 1.33; 95% CI, 1.07–1.66; \( p = 0.01 \)), lower preoperative ALB level (HR, 1.26; 95% CI, 1.07–1.50; \( p = 0.01 \)), and higher preoperative AST level (HR, 1.50; 95% CI, 1.17–1.97; \( p = 0.002 \); Table 3). Independent risk factors for death included later stages of BCLC (HR, 2.21; 95% CI, 1.71–2.85; \( p < 0.001 \)), larger tumor size (HR, 1.85; 95% CI, 1.46–2.33; \( p < 0.001 \)), cirrhosis (HR, 1.66; 95% CI, 1.18–2.33; \( p = 0.004 \)), MVI (HR, 1.50; 95% CI, 1.20–1.88; \( p < 0.001 \)), presence of satellite nodules (HR, 1.50; 95% CI, 1.16–1.95; \( p = 0.002 \)), higher preoperative HBV-DNA load (HR, 1.33; 95% CI, 1.07–1.66; \( p = 0.01 \)), higher preoperative AFP level (HR, 1.46; 95% CI, 1.19–1.79; \( p < 0.001 \)), lower preoperative ALB level (HR, 1.48; 95% CI, 1.20–1.82; \( p < 0.001 \)), and higher preoperative AST level (HR, 1.48; 95% CI, 1.10–1.99; \( p = 0.01 \); Table 3).

4 | DISCUSSION

In this multicenter study, we compared the clinical outcomes of 1303 patients with HBV-related HCC treated
with NtA or NsA therapy after curative resection. We found that NtA therapy was associated with decreased recurrence and increased OS compared to NsA therapy for patients undergoing R0 liver resection of HBV-related HCC. The subgroup analysis revealed that the TDF group had higher RFS and OS rates than the ETV group. This was consistently observed in propensity score-matched and multivariable-adjusted analyses.

Although there has been progress in the management of HCC, the high recurrence rate of tumors remains a major problem for HCC patients undergoing curative resection. There are no internationally recognized effective adjuvant therapies to prevent the postoperative recurrence of HCC. Well-known risk factors for HCC recurrence include advanced BCLC stage, multiple tumors, satellite lesions, large tumors, microvascular invasion, and high HBV load.8,17 For patients with high-risk factors for recurrence, clinical intervention should be actively pursued because these tumor characteristics are not easily improved. In addition to tumor characteristics, inflammation plays a key role in tumorigenesis, and the inflammatory microenvironment is an important part of tumorigenesis.18 Many carcinogenic microbial infections, such as HBV, are associated with some forms of chronic inflammation.19 Therefore, host hepatitis virus load is a correctable risk factor for HCC recurrence after therapeutic resection.8

Previous studies showed that high levels of serum HBV-DNA and HBsAg seropositivity were associated with the development and recurrence of HCC.8,17 Active antiviral therapy with NUCs is an effective treatment for the prevention of HCC recurrence after curative resection.11,12,20 It has been consistently reported that oral treatment with NUCs reduces the risk of postoperative recurrence of HBV-related HCC.10,11,20 The primary mechanism of NUC therapy is inhibition of the activity of HBV polymerase, which halts HBV replication and inhibits the direct and indirect carcinogenic mechanisms of HBV.22 Antiviral therapy prevents HBV reactivation, inhibits hepatitis activity, and reduces the inflammation of liver tissues, which leads to the regression of liver fibrosis and cirrhosis.23 Many recent studies have explored the differential effects of TDF and ETV on risk of HCC in patients with chronic HBV infection. Two meta-analyses and two cohort studies reported that TDF treatment was associated with a lower risk of HCC than ETV treatment.24-27 These studies found that the virological response rate in the early period was higher in patients treated with TDF than in those treated with ETV. This suggests that TDF may have advantages over ETV in terms of the prevention of HCC. Recently, one study showed no significant difference in the rates

**TABLE 2 Multivariate analyses of RFS and OS in HCC patients receiving NsA or NtA therapy after hepatectomy**

| Variables | RFS | | OS | |
|-----------|-----|-----|-----|-----|
| | MV HR (95% CI) | MV p value* | MV HR (95% CI) | MV p value* |
| Age (≤60 vs. >60 years) | 1.22 (1.02–1.48) | 0.03 | 1.23 (0.97–1.56) | 0.09 |
| BCLC stage (B, C vs. 0, A) | 1.30 (1.06–1.61) | 0.01 | 2.06 (1.61–2.62) | <0.001 |
| Group (NtA vs. NsA) | 0.64 (0.51–0.80) | <0.001 | 0.41 (0.29–0.59) | <0.001 |
| Tumor size (>5.0 vs. ≤5.0 cm) | 1.78 (1.51–2.08) | <0.001 | 1.87 (1.51–2.33) | <0.001 |
| Multiple tumors (Yes vs. No) | 1.33 (1.03–1.73) | 0.03 | 0.87 (0.63–1.19) | 0.38 |
| Cirrhosis (Yes vs. No) | 1.52 (1.20–1.92) | <0.001 | 1.70 (1.22–2.37) | 0.002 |
| MVI (Yes vs. No) | 1.52 (1.28–1.80) | <0.001 | 1.48 (1.20–1.82) | <0.001 |
| Capsular invasion (Yes vs. No) | 1.18 (1.02–1.37) | 0.03 | 1.20 (0.99–1.45) | 0.06 |
| Satellite nodules (Yes vs. No) | 1.30 (1.05–1.60) | 0.02 | 1.41 (1.10–1.81) | 0.01 |
| Poor tumor differentiation (Low vs. Intermediate and high) | 1.04 (0.90–1.20) | 0.63 | 1.26 (1.04–1.52) | 0.02 |
| HBV-DNA (>10^3 vs. ≤10^3 IU/ml) | 1.03 (0.89–1.20) | 0.69 | 1.28 (1.04–1.58) | 0.02 |
| AFP (>400 vs. ≤400 ng/L) | 1.16 (0.99–1.35) | 0.053 | 1.46 (1.21–1.77) | <0.001 |
| TB (>17.1 vs. ≤17.1 μmol/L) | 1.15 (0.98–1.35) | 0.09 | |
| ALB (≤40 vs. >40 g/L) | 1.22 (1.04–1.43) | 0.02 | 1.40 (1.15–1.70) | 0.001 |
| ALT (>80 vs. ≤80 U/L) | 0.87 (0.68–1.13) | 0.29 | 0.97 (0.72–1.31) | 0.85 |
| AST (>80 vs. ≤80 U/L) | 1.48 (1.15–1.90) | 0.002 | 1.34 (1.00–1.78) | 0.048 |

Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer staging system; CI, confidence interval; HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival; MV, multivariate; MVI, microvascular invasion; NsA, nucleoside analog; NtA, nucleotide analog; TB, total bilirubin.

*Variables found significant at p < 0.1 in univariable analyses were entered into multivariable Cox regression analyses.
of HCC recurrence and death between the ETV and TDF treatment groups, and two other studies showed that the rates of recurrence and death in the TDF group were significantly lower than those in the ETV group. None of the studies showed that ETV was better than TDF.

The potential mechanism is not clear. However, a recent study by Murata et al. showed that NtA induced the expression of interferon-λ3 (IFN-λ3) and inhibited the production of HBsAg. IFN-λ exhibited effective anti-tumor activity in a mouse model of cancer. IFN-λ3 directly inhibits tumor growth via the induction of apoptosis and/or cell cycle arrest and enhances host immunity by modulating innate and adaptive immune responses. In addition, another study by Murata et al. revealed that only NtA therapy (adefovir dipivoxil [ADV] and TDF) has an additional pharmacological effect in modulating lipopolysaccharide-mediated cytokine production, which was expected to have a favorable immune response to the elimination of HBV. Our result is in line with the research by Choi et al. However, included NtA and NSA therapy, and they included only TDF and ETV therapy. At present, some low-income countries/regions may have problems concerning access to TDF or the high price of TDF. Our study suggests that other NtAs, such as ADV, seem to have the same ability to reduce the risk of HCC recurrence after curative resection. For these cases, we think they can use ADV instead.

Some previous studies suggested that the serum HBV-DNA level or HBsAg seropositivity was an independent risk factor for HCC recurrence and death. Conversely, some studies found that serum HBV-DNA or HBsAg was not associated with prognosis in HCC. Our study found that a higher preoperative serum HBV-DNA level was not an independent risk factor for HCC recurrence, but it was an independent risk factor for death. One possible reason is that all patients were treated with antiviral agents, and the relative risk of viral status was low and was overshadowed by stronger risk factors.

Our study has several limitations. First, this study was a retrospective study. Although we attempted to compensate for potential bias by propensity matching variables associated with treatment outcomes, selection bias remained a possibility. Second, in the subgroup analysis, the TDF group was comprised of much fewer patients than the ETV group because TDF was not approved for use in China until after 2016. Due to limited experience and possible renal
In conclusion, NtA, especially TDF, is a highly potent NUC that effectively reduces HCC recurrence and prolongs postoperative survival. Our study suggests that if patient circumstances permit, NtA therapy, especially TDF, should be preferred in patients with HBV-related HCC after curative resection. Our findings may have considerable clinical significance for the prevention of HCC recurrence in patients.

CONFLICT OF INTEREST
The authors have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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