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Effects of viral load on tenofovir *vs.* entecavir efficacy in recurrence prevention of hepatitis B virus-related hepatocellular carcinoma

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Serum hepatitis B virus deoxyribonucleic acid (HBV-DNA) load is a critical index used to reflect the degree of viral replication in hepatocytes and to evaluate host hepatitis viral status. The risk of hepatocellular carcinoma (HCC) incidence or recurrence varies depending on whether the HBV-DNA load is high or low.[1] Consistent with previous studies and expert opinion, a HBV-DNA level >2000 IU/mL was defined as a high HBV-DNA load in the current study.[2]

Tenofovir disoproxil fumarate (TDF) and entecavir (ETV) have high genetic barriers to drug resistance, exhibit potent viral suppression, and are recommended as first-line therapies in HBV patients. Since low and high HBV-DNA loads represent distinct immune responses to hepatitis B, the impact of either drug on HCC recurrence among patients with low or high HBV-DNA loads remains unclear.

In the current study, we aimed to investigate the difference in TDF *vs*. ETV in preventing HCC recurrence among patients with high or low HBV-DNA loads using a multi-institutional database.

Between 2014 and 2019, the data of 1874 consecutive patients with HBV-related HCC who underwent curative hepatectomy were extracted from three participating medical centers: The People's Hospital of Leshan, Sichuan Provincial People's Hospital, and West China Hospital of Sichuan University. Of these, 922 patients who were treated with TDF or ETV were included in the analysis [Supplementary Figure 1, http://links.lww.com/CM9/B274]. The exclusion criteria were as follows: (1) antitumor treatment before surgery; (2) coinfection with other viruses, such as hepatitis C virus or human immunodeficiency virus; (3) use of interferon or other nucleos(t)ide analogs; (4) history of other malignancies or recurrent HCC; or (5) sequential therapy from nucleos(t)ide analogs to ETV or TDF.

Continuous variables were compared using the *t* test or Mann–Whitney *U* test. Categorical variables were compared using the χ^2 test or Fisher's exact test. Propensity score matching (PSM) was used to minimize the effect of potential confounders. Kaplan–Meier curves were used for comparisons of recurrence-free survival (RFS) between the two treatment groups in the whole cohort and in the PSM cohort. Univariate and multivariate analyses were used to analyze the independent risk factors for RFS using the Cox proportional hazard model.

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. 2021-1151). Given the retrospective nature of the study, the Ethics Committee agreed to waive informed consent.

The baseline characteristics of the 922 patients are presented in Supplementary Table 1, http://links.lww.com/CM9/B275. The mean patient age was 51.8 years, and male patients accounted for 83.6% (771/922). With a median follow-up duration of 34 months, 508 patients (55.0%) developed recurrence. After PSM adjustment, the baseline characteristics were well balanced.

Among 429 patients with low HBV-DNA levels, the RFS in the TDF and ETV treatment groups was not significantly different ($P = 0.160$; Figure 1A). After PSM adjustment, there was no significant difference in the risk of HCC recurrence in either group ($P = 0.220$; Figure 1B).

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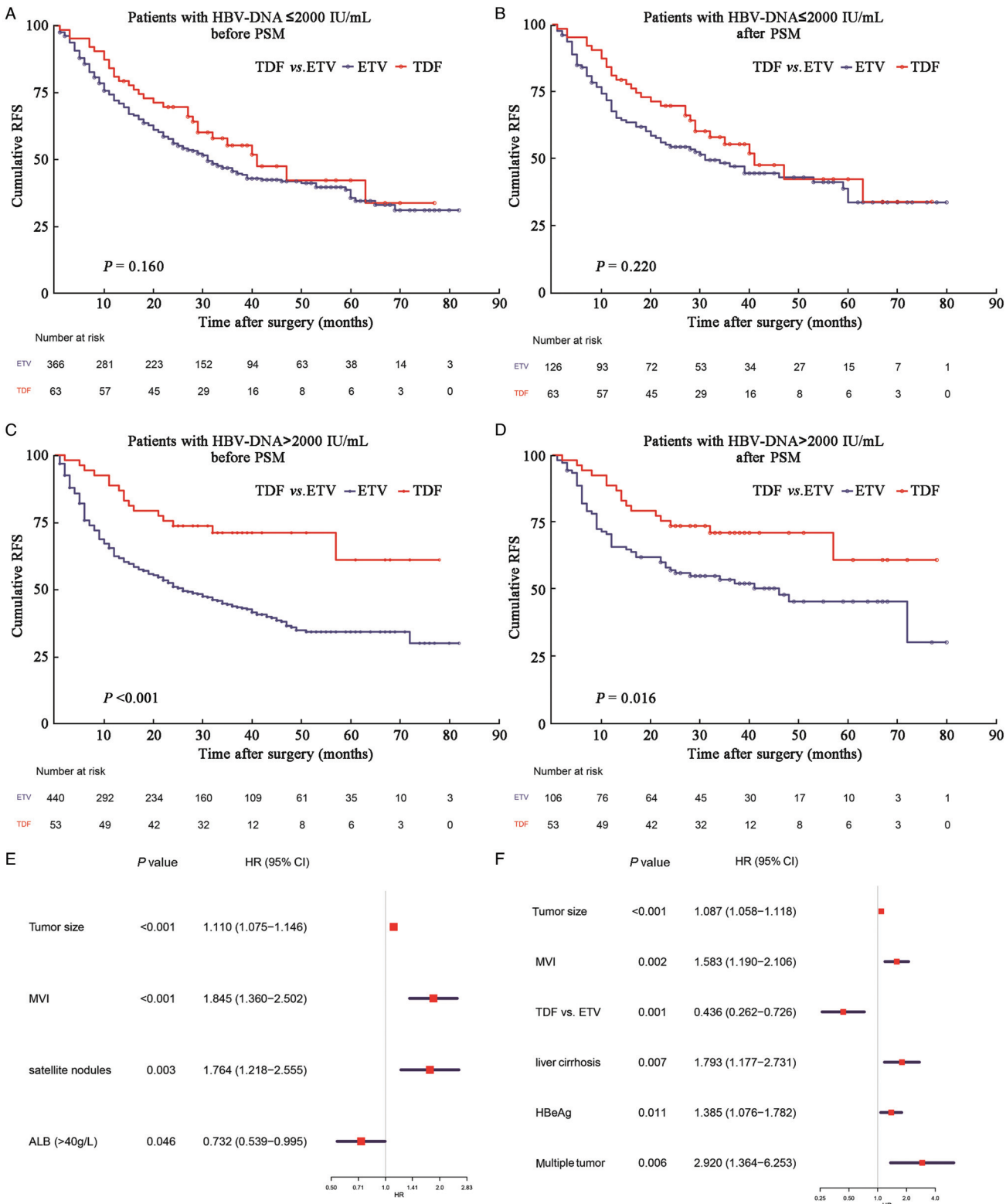

Figure 1: (A) RFS of patients with low HBV-DNA level receiving ETV treatment or TDF treatment. (B) RFS of the propensity score-matched cohort of patients with low HBV-DNA level receiving ETV treatment or TDF treatment. (C) RFS of patients with high HBV-DNA level receiving ETV treatment or TDF treatment. (D) RFS of the propensity score-matched cohort of patients with high HBV-DNA level receiving ETV treatment or TDF treatment. (E) The multivariable Cox regression model of patients with low HBV-DNA level. (F) The multivariable Cox regression model of patients with high HBV-DNA level. CI: Confidence interval; ETV: Entecavir; HBeAg: Hepatitis B E antigen; HBV-DNA: Hepatitis B virus deoxyribonucleic acid; HR: Hazard ratio; MVI: Microvascular invasion; PSM: Propensity score matching; RFS: Recurrence-free survival; TDF: Tenofovir disoproxil fumarate.

The multivariable Cox regression model analysis revealed that the significant factors associated with HCC recurrence were larger tumor size (adjusted hazard ratio [AHR], 1.11; 95% confidence interval [CI], 1.08–1.15; $P<0.001$), microvascular invasion (AHR, 1.85; 95% CI, 1.36–2.50; $P<0.001$), satellite nodules (AHR, 1.76; 95% CI, 1.22–2.56; $P=0.003$), and higher albumin levels (AHR, 0.73; 95% CI, 0.54–1.00; $P=0.046$; Figure 1E).

Among 493 patients with high HBV-DNA levels, the 1-, 3-, and 5-year recurrence rates were 11.3%, 29.0%, and 39.1%, respectively, in the TDF treatment group and 37.7%, 56.4%, and 65.9%, respectively, in the ETV treatment group [Figure 1C]. After PSM adjustment, TDF therapy was still associated with a significantly lower risk of HCC recurrence than ETV therapy ($P=0.016$; Figure 1D). In the multivariable Cox regression model, patients treated with TDF had a significantly longer RFS than those treated with ETV (AHR, 0.44; 95% CI, 0.26–0.73; $P=0.001$) [Figure 1F].

Data on changes in HBV-DNA in 922 patients at 1 year after operation were collected and recorded. We found that the decrease rates of HBV-DNA load in the TDF and ETV groups were 98.3% and 96.2%, respectively, at year 1 [Supplementary Table 1, http://links.lww.com/CM9/B275].

During the follow-up period, 24 patients died in the high-HBV-DNA-load cohort, and 18 patients died in the low-HBV-DNA-load cohort before HCC recurrence. Competing risk analysis showed similar results. In the low-HBV-DNA-load cohort, there was also no difference in the risk of HCC recurrence between TDF and ETV treatment ($P=0.200$; Supplementary Figure 2A, http://links.lww.com/CM9/B274). In the high-HBV-DNA-load cohort, the patients who received TDF therapy still showed a significantly lower risk of HCC recurrence than ETV therapy ($P<0.001$; Supplementary Figure 2B, http://links.lww.com/CM9/B274).

HBV-DNA >2000 IU/mL was a critical cutoff value for guiding antiviral therapy and was associated with the prognosis of HCC patients after hepatectomy.[1,2] In the current study, we found that in patients with low HBV-DNA levels, ETV treatment offered comparable survival to that with TDF. However, among patients with high HBV-DNA levels, TDF treatment appeared to provide more survival benefits than ETV treatment.

In the current study, we found that there was no significant difference in the decrease rate of HBV-DNA load between the TDF and ETV groups at 1 year post-operatively. Similar results were reported in the study by Lee *et al*[3] This suggests that the effects of these two drugs on suppressing HBV and reducing HCC risk are likely to be similar. Therefore, this may be why we observed no difference in the risk of HCC recurrence between TDF and ETV treatment in patients with low HBV-DNA levels. However, we did not observe similar results in patients with high HBV-DNA levels, and another mechanism might explain the difference. Some recent studies have revealed that nucleotide analogs such as TDF can have additional effects on inducing interferon-λ3 expression.[4] Interferon-λ3 was reported to be involved in immunity reactions and antitumor activity.[5] This result suggested that TDF treatment might have additional antitumor effects in HCC. Since there were more aggressive tumors among patients with high HBV-DNA levels, the magnitude of the RFS benefits of TDF might be high.

There were some limitations in our study. First, although there were some proposed mechanisms to explain the differences in both drugs, the mechanism of the superiority of TDF *vs*. ETV remains unclear. The comparison of the percentage of patients in the TDF and ETV treatment groups with the decrease rate of HBV-DNA load was performed at post-operative year 1. Long-term follow-up of the index should be conducted to achieve conclusive results. Second, there were fewer cases in the TDF group. This was because TDF was just approved for use in China in recent years, and many physicians strictly recommended TDF for patients.

In conclusion, TDF treatment is associated with a lower risk of HCC recurrence than ETV treatment in chronic hepatitis B (CHB) patients with high HBV-DNA levels but not in CHB patients with low HBV-DNA levels.

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Conflicts of interest

None.

References

1. Sohn W, Paik YH, Kim JM, Kwon CH, Joh JW, Cho JY, *et al*. HBV DNA and HBsAg levels as risk predictors of early and late recurrence after curative resection of HBV-related hepatocellular carcinoma. Ann Surg Oncol 2014;21:2429–2435. doi: 10.1245/s10434-014-3621-x.
2. Kao JH, Hu TH, Jia J, Kurosaki M, Lim YS, Lin HC, *et al*. East Asia expert opinion on treatment initiation for chronic hepatitis B. Aliment Pharmacol Ther 2020;52:1540–1550. doi: 10.1111/apt.16097.
3. Lee SW, Kwon JH, Lee HL, Yoo SH, Nam HC, Sung PS, *et al*. Comparison of tenofovir and entecavir on the risk of hepatocellular carcinoma and mortality in treatment-naïve patients with chronic hepatitis B in Korea: a large-scale, propensity score analysis. Gut 2020;69:1301–1308. doi: 10.1136/gutjnl-2019-318947.
4. Murata K, Asano M, Matsumoto A, Sugiyama M, Nishida N, Tanaka E, *et al*. Induction of IFN-lambda3 as an additional effect of nucleotide, not nucleoside, analogues: a new potential target for HBV infection. Gut 2018;67:362–371. doi: 10.1136/gutjnl-2016-312653.
5. Syedbasha M, Egli A. Interferon lambda: modulating immunity in infectious diseases. Front Immunol 2017;8:119. doi: 10.3389/fimmu.2017.00119.

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