Tenofovir *vs.* entecavir on recurrence of hepatitis B virus-related hepatocellular carcinoma beyond Milan criteria after hepatectomy

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Abstract

Background: Hepatectomy for hepatocellular carcinoma (HCC) beyond the Milan criteria is shown to be beneficial. However, a high rate of post-operative HCC recurrence hinders the long-term survival of the patients. This study aimed to investigate and compare the impacts of tenofovir (TDF) and entecavir (ETV) on the recurrence of hepatitis B viral (HBV)-related HCC beyond the Milan criteria.

Methods: Data pertaining to 1532 patients who underwent hepatectomy and received antiviral therapy between January 2014 and January 2019 were collected from five centers. Recurrence-free survival (RFS) analysis was performed using the Kaplan–Meier method. Cox proportional hazards regression analysis was performed to determine prognostic factors for HCC recurrence.

Results: The analysis incorporates 595 HBV-related HCC patients. The overall 5-year RFS was 21.3%. Among them, 533 and 62 patients received ETV and TDF treatment, respectively. The 1-, 3-, and 5-year RFS rates were 46.3%, 27.4%, and 19.6%, respectively, in the ETV group compared with 65.1%, 41.8%, and 37.2%, respectively, in the TDF group ($P < 0.001$). Multivariate analysis showed that TDF treatment (hazard ratio [HR]: 0.604, $P = 0.005$), cirrhosis (HR: 1.557, $P = 0.004$), tumor size (HR: 1.037, $P = 0.008$), microvascular invasion (MVI) (HR: 1.403, $P = 0.002$), portal vein tumor thrombus (PVTT) (HR: 1.358, $P = 0.012$), capsular invasion (HR: 1.228, $P = 0.040$), and creatinine levels (CREA) (HR: 0.993, $P = 0.031$) were statistically significant prognostic factors associated with RFS.

Conclusions: Patients with HCC beyond the Milan criteria exhibited a high rate of HCC recurrence after hepatectomy. Compared to the ETV therapy, TDF administration significantly lowered the risk of HCC recurrence.

Keywords: Hepatocellular carcinoma; Hepatitis B virus; Antiviral drugs; Recurrence; Hepatectomy

Introduction

Globally, hepatocellular carcinoma (HCC) is the fifth most common cancer type and the third leading cause of cancer-related deaths. More than 50% of HCC cases are attributed to hepatitis B viral (HBV) infection.[1] In China, due to the high prevalence of HBV infection, the HCC incidence accounts for 42.5% of global HCC cases.[2,3] Curative hepatectomy is recommended for patients at the early stage of HCC.[4] However, 60% of HCC cases in China are first diagnosed at the intermediate to an advanced stage.[2] The tumors in these patients are beyond Milan criteria (a single-tumor ≤5 cm or up to three tumors, all <3 cm, without major vascular invasion), and trans-catheter arterial chemoembolization (TACE) or systemic therapy is recommended. Tumors beyond the Milan criteria include a heterogeneous population, according to either tumor extension (from unifocal HCC to diffused HCC), liver function (from compensated Child-Pugh class A to decompensated liver function), or vascular invasion (from none to branch portal vein tumor thrombus [PVTT] to major PVTT or other major vascular invasions).[5] An increasing amount of evidence suggests that selected

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patients with intermediate to advanced-stage HCC can benefit from surgery.[6-13] In clinical practice, hepatectomy is commonly performed for some patients with HCC beyond the Milan criteria. However, with the expansion of surgical indication, the higher rate of post-operative HCC recurrence has posed a great challenge for patients' survival.[14]

In HBV-related HCC, active viral replication was associated with HCC recurrence after hepatectomy.[15,16] Antiviral therapy could significantly inhibit viral reactivation and improve post-operative recurrence after hepatectomy.[17,18] Entecavir (ETV) and tenofovir (TDF), which were approved for use in China in 2006 and 2014, respectively, are currently the first-line treatment therapy for patients with HBV infection. In recent years, the comparison between both drugs for patients with chronic HBV infection has been a research hotspot. Some investigators strongly regarded that TDF treatment was associated with lower HCC development than ETV treatment,[19,20] whereas some others suggest there were no significant differences between TDF and ETV in their association with HCC incidence.[21,22] Similarly, for hepatectomy patients with early-stage of HBV-related HCC, the conclusions were not in consensus for HCC recurrence after surgery.[23,24] Unlike early-stage HCC, tumors beyond Milan criteria commonly represent a heavy tumor burden and determine HCC recurrence among the patients. Antiviral treatment has been shown to reduce HCC recurrence after treatment for HBV-related HCC. However, the comparison of TDF and ETV, in particular, for better recurrence-free survival (RFS) in HBV-related HCC patients, especially beyond the Milan criteria, remains unclear. The current study was, therefore, designed to investigate TDF *vs*. ETV on reducing the high rate of post-operative recurrence of HCC patients beyond Milan criteria.

Methods

Ethical approval

The study design conformed to the ethical guidelines of the 1975 *Declaration of Helsinki* and was approved by the ethics committee of West China Hospital, Sichuan University (No. 2021-311). The requirement for informed consent was waived due to the retrospective nature of the study.

Participants

The study incorporates retrospective analyses of data pertaining to 1532 patients who underwent hepatectomy between January 2014 and January 2019, sourced from five hospitals. The participating institutions included the Affiliated Hospital of Chengdu University, Affiliated Cancer Hospital of Guizhou Medical University, Sichuan Provincial People's Hospital, the First People's Hospital of Leshan, and West China Hospital of Sichuan University. The inclusion criteria were as follows: (1) age ≥18 years; (2) ongoing use of ETV or TDF; (3) Child-Pugh A/B classes of liver function; (4) up to three tumors, or/and evaluated as a resectable tumor; (5) primary hepatectomy; (6) pathological HCC; (7) positive HBV surface antigen (HBsAg); (8) HCC beyond Milan criteria, and (9) PVTT, vascular invasion limited to a first-order branch of the MPV. The exclusion criteria were as follows: (1) simultaneous malignancies; (2) antitumor therapy before surgery; (3) positive surgical margin; (4) major PVTT or other major vascular involvement; (5) ruptured HCC; (6) lymph node involvement; (7) extrahepatic metastasis, and (8) incomplete follow-up information. Finally, a total of 595 HBV-related HCC patients were included for analyses in the current study [Figure 1].

Data collection and follow-up

The primary liver cancer database in West China Hospital was established in January 2014. All data were prospectively collected using a case report form. The follow-up was conducted through telephonic interviews and using the outpatient records. The quality control of the database was performed at regular intervals by its director. For this study, a uniform datasheet was designed based on the HCC database of our hospital to include the clinicopathological variables from the other four hospitals. The clinicopathological variables, such as tumor size, number, and routine blood tests, were easily available from all the hospitals included in this study. The data entry was carried out by special personnel following uniform standards. Therefore, the integrity and homogeneity of the data were reliable.

In detail, demographic information, including age and gender, and clinicopathological features, including the status of HBV infection, liver function, and tumor-related parameters were collected for all the patients before surgery. Tumor size (cm) and tumor number were reported on pre-operative computed tomography (CT) scans or contrast-enhanced magnetic resonance imaging (MRI) reports. Tumor differentiation, microvascular invasion (MVI), satellite nodules, and surgical margins status were evaluated for the pathological specimens. The degree of fibrosis was graded according to the established classification scheme. Ishak score of 5 or 6 was defined as liver cirrhosis.[25] MVI was defined as the microscopic tumor emboli within the central hepatic vein, the portal vein, or the large capsular vessels. Satellite nodules were defined as tumors ≤2 cm in size that were located within a distance of 2 cm from the main tumor.[26] If the HCC contained poorly differentiated tumor cells, it was classified as poorly differentiated HCC, else as moderate-well differentiated HCC. All pathological examinations were performed by experienced hepatic pathologists.

Based on the current guidelines, antiviral drugs (ETV: 0.5 mg/d or TDF: 300 mg/d) are generally recommended for HBV patients at the first diagnosis. After hepatectomy, follow-up for the patients at post-operative first month and subsequent 3-month intervals in the post-operative 3 years followed by a 6-month interval in consecutive years was conducted. Liver ultrasonography, contrast-enhanced CT, and/or MRI along with serum tumor marker alpha-fetoprotein (AFP) were performed during the follow-up. HCC recurrence was diagnosed based on findings of two typical imaging tests, or one imaging technique showing

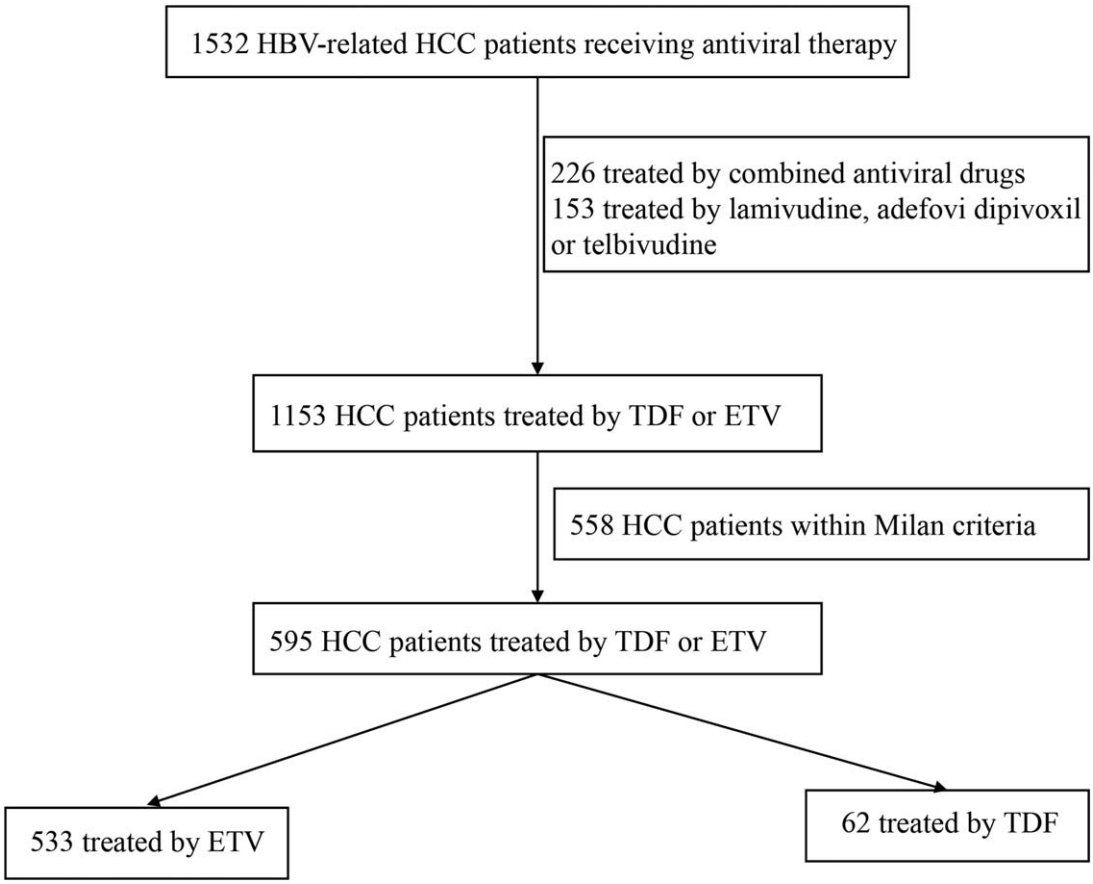

Figure 1: The selection process of patients in the study. ETV: Entecavir; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; ICC: Intrahepatic cholangiocarcinoma; TDF: Tenofovir.

typical features of HCC along with AFP level >400 ng/mL, or by biopsy/resection. Treatment for recurrent HCC included salvage liver transplantation, repeat hepatectomy, radiofrequency ablation (RFA), TACE, sorafenib, and best supportive care. The re-treatment regimen was recommended by a multidisciplinary team composed of a hepatic surgeon, hepatologist, oncologist, pathologist, and radiologist. RFS was defined as the time interval between the surgery and the first instance of the detectable recurrence. The last follow-up was at the end of March 2021, or until death. The lost follow-up rate was approximately 12.5%.

Statistical analysis

Continuous data were presented as mean (interquartile range) and compared using the Mann–Whitney *U* test. Categorical variables were expressed as numbers (frequency) and compared using χ^2 or Fisher exact tests, as appropriate. The RFS was calculated using the Kaplan–Meier method and compared using the log-rank test. To further investigate the impact of antiviral drugs on HCC recurrence, the inverse probability treatment weight (IPTW) analysis was performed. The survival difference in both groups was obtained after adjusting for other prognostic factors by assigning a weight of 1 to cases in the TDF group and propensity score (PS)/(1–PS) to cases in the ETV group. Cox proportional hazards regression analysis was performed to determine prognostic factors for HCC recurrence. Variables with $P < 0.050$ in the univariate analysis were subsequently included in the multivariate analysis. All statistical analyses were performed using the SPSS statistical package (version 20.0; SPSS Inc., Chicago, IL, USA) and R software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). $P < 0.050$ was defined as statistically significant.

Results

Baseline characteristics

As shown in Table 1, among 595 patients, 533 (89.6%) patients underwent treatment with ETV and 62 (10.4%) with TDF. One hundred and thirty one (22.0%) patients were >60 years of age, and 502 patients (84.4%) were male. In 409 patients (68.7%), HBV-DNA detected was >1000 IU/mL and 130 patients (21.8%) tested positive for hepatitis B e antigen (HBeAg). The mean tumor size of HCC was 8.5 cm, and 95 patients (16.0%) had multiple tumors. One hundred and forty two patients (23.9%) had branch portal vein thrombus. Liver cirrhosis was present in 502 (84.4%) patients. The presence of MVI and capsular invasion was found in 228 patients (38.3%) and 311 (52.3%), respectively. Ninety one patients (15.3%) had satellite nodules. Poorly differentiated tumors could be observed in 295 patients (49.6%). Antiviral treatment was initiated among all the patients before the surgery.

Compared with the ETV group, patients with high serum albumin (ALB) levels (≥40 g/L) were much more in the TDF group (82.3% *vs.* 66.8%; $P = 0.020$). Despite absence of statistically significant differences, it was found that the TDF group had a higher rate of PVTT (30.6% *vs.* 23.1%), multiple tumors (19.4% *vs.* 15.6%), and alanine aminotransferase (ALT) >50 U/L (53.2% *vs.* 46.0%), and lower rate of satellite nodules (9.7% *vs.* 15.9%), HBV-DNA >1000 U/mL (61.3% *vs.* 69.6%), aspartate transaminase (AST)>40 U/L (56.5% *vs.* 61.4%), and fewer patients aged >60 years (16.1% *vs.* 22.7%) [Table 1].

HCC recurrence and survival

Until the last follow-up, 418 patients (70.2%) had a recurrence and 289 (48.6%) were dead. For patients with HCC beyond the Milan criteria who underwent hepatectomy, the 1-, 3-, and 5-year overall survival (OS) rates were 73.8%, 51.5%, and 44.7%, respectively, and the 1-, 3-, and 5-year RFS rates were 48.3%, 28.9%, and 21.3%, respectively. Among 418 patients, a total of 369 patients (88.1%) suffered from HCC recurrence within 2 years. For these patients with early recurrence (ER), the 1-, 3-, and 5-year OS rates were 62.5%, 29.3%, and 21.6%, respectively ($P < 0.001$) [Figure 2].

Comparison of TDF and ETV treatments for HCC recurrence

Across the entire cohort, HCC recurrence was observed in 383 (64.4%) patients in the ETV group and 35 (56.5%) in the TDF group during the follow-up period. The 1-, 3-, and 5-year RFS rates were 46.3%, 27.4%, and 19.6%, respectively, in the ETV group as compared to 65.1%, 41.8%, and 37.2%, respectively, in the TDF group ($P = 0.007$) [Figure 3].

Clinical variables, including age, gender, tumor size, multiple tumors, PVTT, liver cirrhosis, MVI, capsular invasion, satellite nodules, tumor differentiation, HBV-DNA, HBeAg, AFP (>400 ng/mL), prothrombin time, platelet-to-lymphocyte ratio (>107.1), neutrophil-to-lymphocyte ratio (>2.7), ALB (>40 g/L), ALT (>40 U/L), AST (>40 U/L), and total bilirubin (>28 μmol/L) were adjusted in the IPTW analysis. The results were consistent in that the patients in the TDF group were found to have a lower risk of HCC recurrence than the ETV group (1-, 3-, and 5-years: 70.3%, 37.4%, and 37.4% *vs.* 50.8%, 27.6%, and 19.6%; $P = 0.006$) [Figure 3].

Prognostic factors associated with HCC recurrence

The results of univariate and multivariate analyses are summarized in Figure 4. From the univariate analysis, age (>60 years), HBeAg, ALB (>40 g/L), AST (>40 U/L), TDF treatment, liver cirrhosis, tumor size, MVI, satellite nodules, PVTT, capsular invasion, AFP (>400 ng/mL), and creatinine levels (CREA) were identified as significant factors [Figure 4A]. From the multivariable analysis, liver cirrhosis (hazard ratio [HR], 1.557, $P = 0.004$), tumor size (HR, 1.037, $P = 0.008$), MVI (HR, 1.403, $P = 0.002$), PVTT (HR, 1.358, $P = 0.012$), capsular invasion (HR,

Table 1: Baseline characteristics in whole cohort of HBV-related HCC patients.

Characteristics	Overall ($n = 595$)	ETV group ($n = 533$)	TDF group ($n = 62$)	Statistics	*P* value
Age (>60 years)	131 (22.0)	121 (22.7)	10 (16.1)	1.041*	0.308
Gender (male)	502 (84.4)	450 (84.4)	52 (83.9)	<0.001*	1.000
HBeAg	130 (21.8)	115 (21.6)	15 (24.2)	0.096*	0.757
HBV-DNA (>10^3 IU/mL)	409 (68.7)	371 (69.6)	38 (61.3)	1.421*	0.233
Liver cirrhosis	502 (84.4)	446 (83.7)	56 (90.3)	1.390*	0.238
Tumor size (cm)	8.5 (6.4, 12.0)	8.5 (6.3, 12.0)	8.3 (6.5, 11.0)	0.758†	0.384
Multiple tumor	95 (16.0)	83 (15.6)	12 (19.4)	0.344*	0.558
MVI	228 (38.3)	205 (38.5)	23 (37.1)	0.005*	0.943
Capsular invasion	311 (52.3)	276 (51.8)	35 (56.5)	0.316*	0.574
Satellite nodules	91 (15.3)	85 (15.9)	6 (9.7)	1.236*	0.266
Tumor differentiation				0.570*	0.752
Well	2 (0.3)	2 (0.4)	0		
Moderate	298 (50.1)	269 (50.5)	29 (46.8)		
Poorly	295 (49.6)	262 (49.2)	33 (53.2)		
PVTT	142 (23.9)	123 (23.1)	19 (30.6)	1.359*	0.244
AFP (>400 ng/mL)	292 (49.1)	263 (49.3)	29 (46.8)	0.062*	0.804
TBIL (>28 μmol/L)	20 (3.4)	20 (3.8)	0	1.391*	0.238
ALT (>40 U/L)	278 (46.7)	245 (46.0)	33 (53.2)	0.902*	0.342
AST (>40 U/L)	362 (60.8)	327 (61.4)	35 (56.5)	0.373*	0.541
ALB (>40 g/L)	407 (68.4)	356 (66.8)	51 (82.3)	5.452*	0.020
PT (s)	12.1 (11.5, 12.9)	12.1 (11.5, 12.9)	12.1 (11.3, 12.8)	0.892†	0.345
†PLR (>107.1)	298 (50.1)	266 (49.9)	32 (51.6)	0.014*	0.904
‡NLR (>2.7)	255 (42.9)	227 (42.6)	28 (45.2)	0.063*	0.801
CREA (μmol/L)	68.0 (59.0, 79.0)	67.7 (59.0, 79.0)	70.5 (61.3, 81.0)	2.066†	0.151

Continuous variables were shown as median (interquartile range), and categorical variables were shown as number (frequency). * χ^2 test, †Mann-Whitney *U* test, ‡Cut-off value was defined as the mean value. AFP: Alpha-fetoprotein; ALB: Albumin; AST: Aspartate transaminase; CREA: Creatinine levels; ETV: Entecavir; HBV: Hepatitis B viral; HCC: Hepatocellular carcinoma; HBeAg: Hepatitis B e antigen; MVI: Microvascular invasion; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; PVTT: Portal vein tumor thrombus; TDF: Tenofovir; TBIL: Total bilirubin.

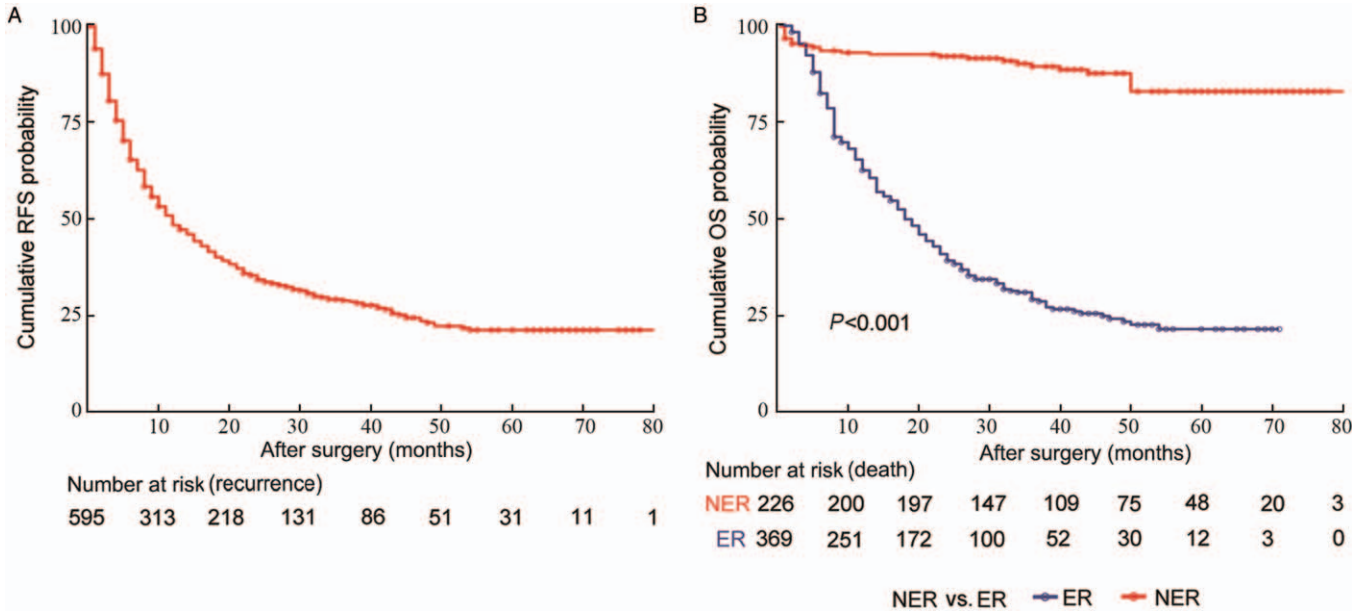

Figure 2: RFS analysis in the whole cohort. (A) Cumulative RFS in HCC patients beyond the Milan criteria. (B) Cumulative OS in patients with or without ER (within 2 years) after surgery. ER: Early recurrence; HCC: Hepatocellular carcinoma; NER: Non-early recurrence; OS: Overall survival; RFS: Recurrence-free survival.

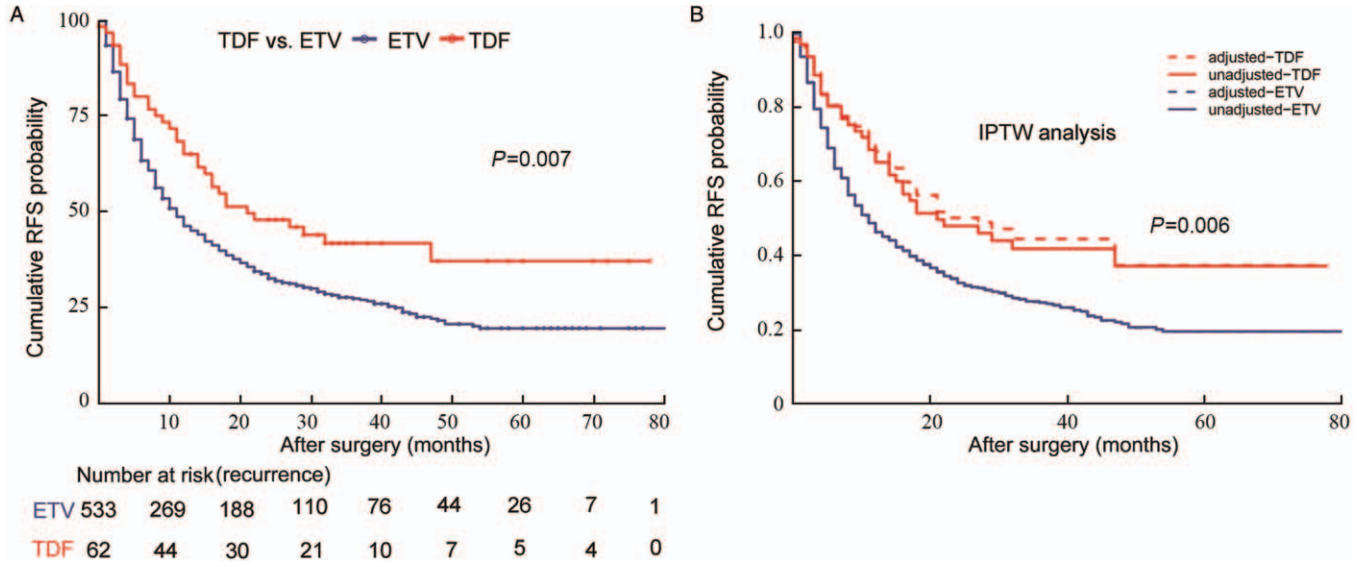

Figure 3: RFS comparison stratified by TDF and ETV. (A) Cumulative RFS in patients with TDF or ETV after surgery. (B) Cumulative RFS in patients with TDF or ETV after adjusting for other prognostic factors in IPTW analysis. ETV: Entecavir; IPTW: Inverse probability treatment weight; RFS: Recurrence-free survival; TDF: Tenofovir.

1.228, $P = 0.040$), and CREA levels (HR, 0.993, $P = 0.031$) were identified as the significantly associated prognostic factors for RFS. Interestingly, TDF treatment was a favorable factor that was significantly associated with HCC recurrence (HR, 0.604; 95% confidence interval, 0.427–0.856; $P = 0.005$) as compared to ETV therapy [Figure 4B].

Discussion

In the entire cohort consisting of 595 patients, we found that at a median follow-up time of 28.5 months, there were 177 (19.2%) patients who did not develop recurrence. Overall, the 3- and 5-year survival rates were 51.5% and 44.7%, similar to findings of a previous randomized controlled trial (RCT).[27] The rate of OS provided by hepatectomy in selected patients was much higher than that of TACE.[8,27] Our results confirmed that patients with HCC beyond the Milan criteria could benefit from hepatectomy. After R0 hepatectomy, reducing and even avoiding the chances of tumor recurrence is a big obstacle for long-term survival. Among HCC patients, estimates suggest that the 5-year recurrence rate could reach up to 70%. In the current study, 21.3% of patients had tumor RFS in 5 years. The high HCC recurrence rate leads to an unsatisfactory long-term survival. Patients with ER had a

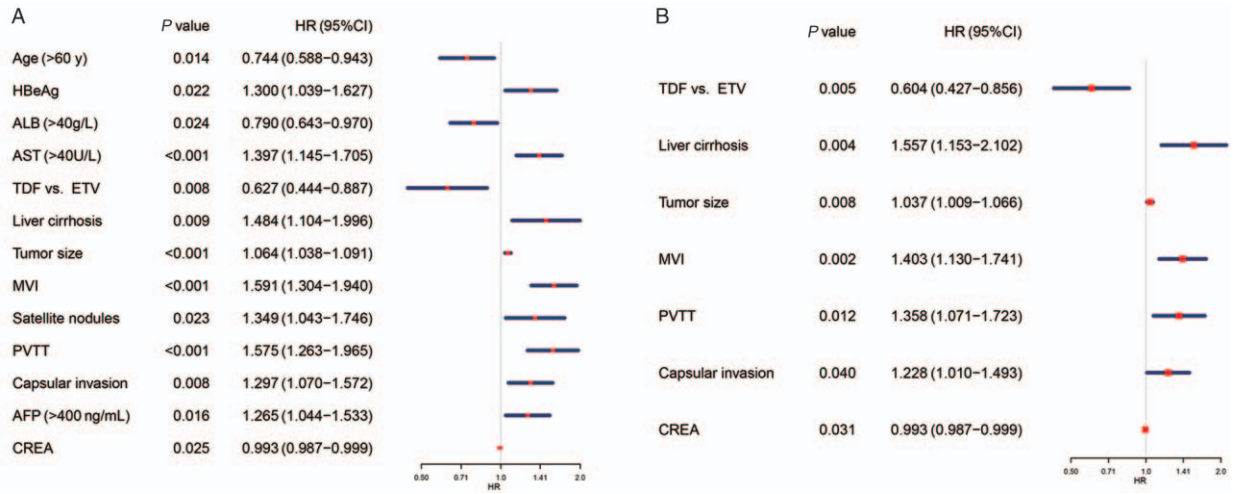

Figure 4: Independent prognostic factor analyses. (A) Univariate analysis of the prognostic factors related to HCC recurrence. (B) Multivariate analysis of the prognostic factors related to HCC recurrence. AFP: Alpha-fetoprotein; CREA: Creatinine levels; ETV: Entecavir; HCC: Hepatocellular carcinoma; HR: Hazard ratio; MVI: Microvascular invasion; PVTT: Portal vein tumor thrombus.

5-year OS of only 21.6%. As reported in previous studies, there was a close relationship between HBV and HCC. Chronic HBV infection was a major risk factor for the development of HCC. Chronic inflammation and the release of cytokines largely contribute to the development of liver cell proliferation and malignant transformation. In addition, HBV-DNA integration into the host genome can induce both genomic instability and direct insertional mutagenesis of diverse cancer-related genes.[28] Several studies show that antivirus therapy can reduce HCC development.[18] Moreover, a high HBV load was related to HCC recurrence after RFA.[29]

In the current study, we included all patients with HBV infection. Therefore, from an etiological perspective, it was of critical significance to compare the underlying role of TDF *vs*. ETV in HCC recurrence. Interestingly, we found that TDF treatment showed a lower recurrence rate than ETV treatment (HR:0.604). Regarding prevention of tumor recurrence through both drugs, two studies have reported differing results as follows: one study including 726 patients treated by RFA or resection shows that there is no difference in HCC recurrence, whereas another study including 1695 early-stage HCC patients suggests that TDF had an advantage over ETV for prevention of HCC recurrence.[23,24] The differences may be rooted in the different patient cohorts; the first study included patients receiving RFA or resection. Based on these reports, both treatments had different impacts on HCC recurrence. In our study, we limited our cohort to include the patients with HCC beyond the Milan criteria undergoing hepatectomy only. Additionally, drug switching may occur in HBV management due to higher drug resistance for TDF. Currently, we included all patients who had an ongoing treatment course of ETV or TDF. Since there is a lack of well-designed studies like RCTs, this debate may continue for a longer time. Patients with HCC beyond the Milan criteria suffered from a higher HCC recurrence after surgery. Every treatment method for reducing postoperative recurrence deserves further investigation. We showed that the TDF therapy was associated with better RFS than the ETV therapy. As to the baseline characteristic comparisons, there was a significant statistical difference in the serum albumin levels. The TDF group had younger patients with major vascular invasion and less presence of satellite nodules. To better understand the differences in roles of both antiviral drugs for RFS, we adjusted for the clinical variables except for the antiviral treatment regimen and then compared the RFS differences using IPTW analysis. The model has a good performance as it avoids the effects of cofounders and is widely utilized for prognoses comparisons.[23] Consistently, the results also supported the advantage of TDF over ETV. Despite the wide difference between the sample size of both groups, we consecutively collected the patient information treated by TDF or ETV beginning from January 2014. All the patients had initiated the use of ETV or TDF drugs; the median follow-up time was also comparable. Additionally, our cohort patients were obtained from academic teaching institutes. All the abovementioned reasons may increase the reliability of our conclusions.

There are some possible mechanisms to explain the differences between TDF and ETV. Both the antiviral drugs belong to nucleoside and nucleotide analogs, respectively. A clinical study shows that nucleotide analogs can induce a rise in the serum interferon-λ3 (IFN-λ3) levels.[30] IFN-λ has antitumor effects on hepatoma.[31] TDF has a higher genetic barrier to drug resistance than ETV, which can lead to better control over virus replication for a relatively long time.[32] However, there are some contrasting opinions. For example, a previous study[33] suggests that it remains unclear whether long-term TDF use can induce IFN-λ3 production. The relationship between IFN-λ3 and HCC incidence has not been fully identified.[24] In patients who receive such highly potent antiviral drugs like TDF or ETV, the difference in their viral responses, particularly under strict follow-up, may be insufficient to cause such differences in the risk of HCC progress.[22] Therefore, the mechanisms of TDF superiority over ETV need further investigation.

Previous studies show that high serum HBV-DNA levels and HBeAg seropositivity are independent risk factors for HCC recurrence and death.[15,16] However, in the current study, serum HBV-DNA levels and HBeAg seropositivity were not identified as independent risk factors for HCC recurrence. The possible reason could be that the HCC was well managed by highly potent antiviral drugs. The relative risk of viral status was relatively low and was possibly compensated by other strong risk factors. In this study, we also found that cirrhosis was associated with a higher rate of HCC recurrence (HR: 1.557). Previous studies do not show the role of cirrhosis in HCC prognosis after hepatectomy.[9,13,27] This may be due to the treatment of all patients using antiviral drugs, resulting in good control of viral replication, and thus the role of liver cirrhosis in HCC recurrence became prominent in our findings. Additionally, we also found that some other variables were associated with HCC recurrence, including the tumor size, PVTT, MVI, and capsular invasion. Tumor size was a critical determinant of HCC recurrence. Vascular invasion is the key event that determines the rate of HCC recurrence and extrahepatic metastases after hepatectomy.[34] The presence of vascular invasion commonly indicates the possible spread of cancer cells through the vascular route.

In conclusion, for the high rate of tumor recurrence for patients beyond the Milan criteria, TDF therapy seemed to offer better RFS than ETV therapy. The findings could guide the antiviral therapeutic regime for this specific stage of HCC.

However, the study has some limitations. First, the retrospective nature was associated with a possible selection bias, particularly in terms of recommendations for the antiviral drugs. RCTs are required to confirm the differences in the prognoses of HCC. Second, there were fewer cases in the TDF group, which could have resulted in a selection bias. This was because the TDF was approved for use in China in recent years and many physicians strictly recommended TDF for patients with co-morbidities. Third, we did not fully consider post-operative adjunctive therapy as the treatment choices varied greatly. Finally, since ETV and TDF are highly potent antiviral drugs, the HBV replication is well under control and patients are under strict follow-up. However, we did not consider the potential impact of viral response in the prognosis of HCCs.

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Conflicts of interest

None.

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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