Impact of Tenofovir Alafenamide Vs. Entecavir on Hepatocellular Carcinoma Risk in Patients With Chronic Hepatitis B

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Abstract

Background & aims: Whether entecavir (ETV) or tenofovir alafenamide (TAF) is better at preventing hepatocellular carcinoma (HCC) development among patients with chronic hepatitis B (CHB) remains unclear. The present study was conducted to explore the ability of these two antivirals to prevent HCC.

Methods: From 2012 to 2019, treatment-naïve CHB patients undergoing ETV or TAF therapy were recruited at three academic teaching hospitals. The TAF group comprised patients starting TAF as first-line antiviral and those switching antivirals from tenofovir disoproxil fumarate to TAF. Patients with decompensated cirrhosis or HCC at enrollment were excluded from the analysis. Cumulative probabilities of HCC were assessed using the Kaplan-Meier method.

Results: In total, 1,810 patients (1,525 and 286 in ETV and TAF groups, respectively) were recruited. The annual HCC incidence was statistically not different between the ETV and TAF groups (1.67 *vs*. 1.19 per 100 person-years, respectively) with an adjusted hazard ratio (HR) of 0.681 (p=0.255), as determined by multivariate analysis. Male, hypertension, liver cirrhosis, FIB-4 index, and albumin were independent prognostic factors for HCC development. Propensity score-matched and inverse probability of treatment weighting analyses yielded similar results, with non-statistically different HCC incidence between the ETV and TAF groups (1.07 *vs.* 1.19 per 100 person-years (HR=0.973; p=0.953) and 1.67 *vs.* 1.89 per 100 person-years, respectively (HR=0.949; p=0.743).

Conclusions: These findings suggest that ETV- and TAF-treated CHB patients have similar risk of developing HCC. Further studies with the larger sample size and longer follow-up are needed to validate these results.

Introduction

Chronic hepatitis B virus (HBV) infection affects approximately 350 million people worldwide, and chronic hepatitis B (CHB) is endemic to East Asia. [1–5] Given the persistent intrahepatic replication status of HBV-DNA, HBV infection itself is significantly associated with increased risk of liver disease progression to cirrhosis and/or hepatocellular carcinoma (HCC). [6, 7] Therefore, replication-suppressing antiviral therapy with potent nucleos(t)ide analogues (NUCs) and high genetic barrier to resistance is recommended to patients with chronic HBV infection in order to prevent liver disease progression. [2] Nevertheless, as the HBV-DNA integrates into the host hepatocyte genome, the virus is rarely eradicated through long-term antiviral therapy, and most patients with CHB additionally require periodic HCC surveillance. [8, 9]

Recently, along with entecavir (ETV) and tenofovir disoproxil fumarate (TDF), tenofovir alafenamie (TAF) was accepted as first-line NUC for the treatment of older populations or patients with co-morbidities for renal or bone disease. This approval was based on the similar short to intermediate-term antiviral effects of these three agents in treatment-naïve CHB patients. [10, 11] Furthermore, effective rescue regimens may offset the potential hazard by suboptimal virological response or genotypic resistance even in a very

small proportion (approximately 1%) of patients treated with ETV. [12, 13] Accordingly, the long-term clinical efficacy for preventing the risk of liverdisease progression to cirrhosis and/or HCC are expected to be similar among the regimens. Nevertheless, since Choi *et al*. [14] reported that TDF is associated with a significantly lower risk of HCC (hazard ratio [HR] = 0.61) and all-cause mortality or orthotopic liver transplant (HR = 0.77) than ETV, several studies were conducted to validate such phenomena. However, this issue remains controversial due to somewhat contradictory results among studies, including similar efficacy between patients receiving two antivirals, overall favorable outcomes among those treated with TDF, or discrepant results according to presence of cirrhosis or follow-up duration. [15–20] In addition, a more recent study based on data from two phase III clinical trials [21, 22] showed that patients treated with TAF showed a tendency for lower risk of HCC development, even though not statistically significant ($p = 0.14$), compared to those treated with TDF. [23]

The present large-scale, multicenter cohort study was conducted in three academic teaching hospitals in the Republic of Korea aiming to further explore the efficacy of ETV- and TAF-based treatment in treatmentnaïve CHB patients, regarding the risk of HCC development.

Methods

Subjects

Treatment-naïve CHB patients who underwent antiviral therapy with either ETV 0.5 mg/day (ETV group) or TAF 25 mg/day-based regimen (TAF group) from 2012 to 2019 in three academic teaching hospitals (Yonsei University Severance Hospital, Kyungpook National University Hospital, and Chung Ang University Hospital) were consecutively screened for eligibility. TAF group comprised patients starting TAF as a first-line antiviral regimen as well as those who switched NUCs from the TDF to the TAF regimen. The inclusion criteria were as follows: (1) age ≥ 19 years, (2) well-preserved liver function, and (3) follow-up duration of at least 6 months. The exclusion criteria were as follows: (1) history of HCC at enrollment, (2) decompensated cirrhosis at enrollment, (3) change of antiviral from ETV to TDF or TAF, (4) change of antiviral from TDF or TAF to ETV, (5) coinfection with other hepatitis virus, (6) history of organ transplantation, (7) development of clinical events (HCC, death, or orthotopic liver transplant) within 6 months of enrollment, and (8) other significant medical illnesses. Owing to the homogenous nature of the study population, data on race/ethnicity were not collected.

In the Republic of Korea, the reimbursement criteria for ETV, TDF, or TAF are identical (**Supplementary Table 1**). If histologic information was not available, compensated cirrhosis was clinically defined according to the following criteria: (1) platelet count < 150,000/μL and ultrasonographic findings suggestive of compensated cirrhosis, including a blunted, nodular liver surface accompanied by splenomegaly (> 12 cm); or (2) esophageal or gastric varices.

The study protocol was consistent with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of each participating institution.

Clinical evaluation, follow-up, and outcomes

During follow-up, all patients underwent routine blood-chemistry testing, and serum HBV-DNA levels and of other viral markers were assessed every 3–6 months. Patients also evaluated by ultrasonography and the serum levels of alphafetoprotein were determined every 6 months to screen for HCC and cirrhotic complications. [24–26]

The primary outcome of the study was HCC development, as diagnosed based on histological evidence or dynamic computed tomography, and/or magnetic resonance imaging findings (nodule > 1 cm with arterial hypervascularity and portal/delayed-phase washout). [27–30] The index date was the date of the first antiviral prescription and the time to HCC development was considered as the period between the index date and the date of HCC diagnosis or the end of follow-up in the absence of HCC development.

Statistical analysis

Data are expressed as means ± standard deviation or as numbers (%). Differences among continuous and categorical variables were examined for statistical significance using the Student's *t*test (or the Mann–Whitney test, if appropriate) and the chi-squared test (or Fisher's exact test, if appropriate). The cumulative risk of HCC was calculated using the Kaplan–Meier method and was compared using the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model.

To reduce selection bias and the effect of potential confounders, propensity scores (PS) were calculated by logistic regression based on age, gender, diabetes, hypertension, compensated cirrhosis, hepatitis B e-antigen (HBeAg), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, and platelet count. Differences between the ETV and TAF groups were balanced by a 1:1 PS-matched and inverse probability of treatment weighting (IPTW) analyses.

All statistical analyses were conducted using the SAS (ver. 9.4; SAS Institute, Cary, NC, USA) and R software (V.3.4.4, http://cran.r-project.org/). Two-sided *p*-values < 0.05 were deemed statistically significant differences.

Results

Baseline characteristics

A total of 1,810 patients were included in the analyses, among whom 1,525 and 285 were comprised in the ETV and TAF groups, respectively. The baseline characteristics of the patients are listed in **Table 1**. Patients in the ETV group were older (52.3 vs. 49.5 years, $p < 0.001$) and a higher proportion of patients had diabetes (18.0% vs. 9.5%, $p < 0.001$) and hypertension (23.3% vs. 16.5%, $p = 0.011$) and a lower proportion were HBeAg-positive (34.3% vs. 56.8%, $p < 0.001$), compared to those in the TAF group, respectively. Moreover, the TAF group had higher mean platelet count (179.4 *vs.* 178.9 ´ 10^3/mL; $p < 0.001$) and albumin levels (4.1 vs. 4.0 g/dL, $p < 0.001$) and lower total bilirubin level (1.0 vs. 1.1 mg/dL, $p < 0.001$), compared to the ETV group, respectively. However, no significant difference in the proportion of

males (60.0% vs. 59.6%, $p = 0.912$) and liver cirrhosis (29.0% vs. 33.7%; $p = 0.116$) was observed between the groups.

Clinical outcomes and comparison of baseline characteristics between patients with HCC and those without

Among the entire cohort, 89 (4.9%) patients developed HCC during follow-up, of whom 79 (5.2%) were in the ETV group and 10 (3.5%) were in the in the TAF group ($p = 0.231$). Patients with HCC were more likely to be older (56.9 vs. 52.1 years, $p < 0.001$) and male (83.1% vs. 58.7%, $p < 0.001$) and have hypertension (46.1% vs. 21.0%, $p < 0.001$), liver cirrhosis (48.3% vs. 28.8%, $p < 0.001$), and lower mean platelet counts (137 vs. 181 ´ 10^3/mL, $p < 0.001$), compared to patients without HCC, respectively (**Supplementary Table 2**).

The cumulative risk of HCC development at 1, 3, and 5 years was 0.8%, 4.3%, and 10.7% (annual incidence, 1.67 per 100 person-years), respectively, in the ETV group; and 0.0%, 1.4%, and 10.6% (annual incidence, 1.19 per 100 person-years), respectively, in the TAF group ($p = 0.252$) (**Figure 1**), representing a HR (reference: ETV group) of 0.681 (95% confidence interval [CI]: 0.351–1.320; $p = 0.255$).

Prognostic factors affecting HCC development

Table 2 shows the potential risk factor for HCC development. Male, diabetes, hypertension, liver cirrhosis, FIB-4 index, and albumin levels, but not TAF group, proved to be significant risk factors for HCC development according to univariate analysis. After adjusting such significant univariate predictors, the risk of HCC was not statistically different between the two groups (adjusted HR = 0.646 [95% CI: 0.331–1.258]; $p = 0.198$).

Next, these identified potential risk predictors were further assessed by multivariate analysis, which revealed that male (adjusted HR = 3.796 [2.159–6.674]; $p < 0.001$), hypertension (adjusted HR = 3.042 [1.935–4.783]; $p < 0.001$), liver cirrhosis (adjusted HR = 1.801 [1.184–2.739]; $p = 0.006$), FIB-4 index (adjusted HR = 1.084 [1.029–1.142]; $p = 0.002$), and albumin (adjusted HR = 0.954 [0.633–1.438], $p = 0.823$) were the independent prognostic factors for HCC development.

Clinical outcomes after adjustment by PS-matching

The 1:1 PS-matched analysis generated 285 pairs, of which the standardized mean differences of all variables converged upon almost 0.1 (**Supplementary Figure 1**), suggesting the appropriate balancing of the variables between the ETV and TAF groups. The baseline characteristics of the two groups are described in **Table 3**. No significant difference in any variables were observed between the groups (all $p > 0.05$), except for AST and ALT levels (both $p < 0.001$). The cumulative risk of HCC development at 1, 3, and 5 years was of 0.7%, 2.6%, and 5.8% (annual incidence: 1.07 per 100 person-years) in the ETV group and was 0.0%, 1.3%, and 10.6% (annual incidence: 1.19 per 100 person-years) in the TAF group (**Figure 2**; $p = 0.952$), respectively, representing a HR of 0.973 [95% CI: 0.400–2.368] ($p = 0.953$).

Clinical outcomes after adjustment by IPTW

The standardized mean differences of all variables after IPTW also converged upon almost 0.1 (**Supplementary Figure 2**), suggesting the appropriate balancing of the variables between the ETV and TAF groups. The baseline characteristics of the two groups were described in **Table 4**. No significant differences were observed for most variables between the ETV and TAF groups (all $p > 0.05$), except for age ($p < 0.001$), liver cirrhosis ($p = 0.034$), and the levels of AST ($p < 0.001$), ALT ($p < 0.001$), total bilirubin ($p = 0.040$), and albumin ($p = 0.001$). The cumulative risk of HCC development at 1, 3, and 5 years was of 0.8%, 4.3%, and 10.6% (annual incidence: 1.67 per 100 person-years) in the ETV group and 0.0%, 2.7%, and 17.2% (annual incidence: 1.89 per 100 person-years), in the TAF group (**Figure 3**; $p = 0.869$), respectively, representing a HR of 0.949 [95% CI: 0.696–1.295] ($p = 0.743$).

Discussion

The current guidelines recommend ETV, TDF, or TAF as first-line NUCs against chronic HBV infection, based on similar efficacies of virological, serological, and biochemical response. [2, 3] Of these, considering renal and bone safety during long-term NUC therapy, ETV or TAF might be preferred for the treatment of the so-called “high-risk” patients. In line with the ongoing controversy about which is better between ETV vs. TDF for preventing HCC development, the most recent study showed a trend that TAF has a more favorable preventive effect than TDF. [23] Given the poor prognosis of HCC, determining the treatment of choice for patients with CHB could become a scientifically, socio-economically, and ethically important matter. Hence, in our independent, large-scale, multi-center cohort study, this issue was addressed.

The present study showed that prescribing TAF as a first-line NUCs or switching NUCs from TDF to TAF did not provide a statistically significant benefit over long-term ETV as a first-line treatment, as demonstrated by the comparable clinical outcomes regarding HCC development in all the analyses performed (including not only unadjusted analysis but also multivariate, PS-matched, and IPTW analyses; all $p > 0.05$). This study had several strengths. First, the large sample of approximately 1,800 patients from three independent academic teaching hospitals enhanced the reliability of the results. Considering that TAF has been officially reimbursed by the National Health Insurance Service of the Republic of Korea since November 2017, the relatively sufficient number of HCC cases (4.3%) with a median follow-up period of 35.7 months in the present study contrast with the 1.3% HCC incidence reported by Lim *et al.*, [23] thereby providing adequate statistical power to address this issue. [29] Second, in order to minimize the confounding effects through the change of medication from ETV to TDF/TAF, or vice-versa, owing to poor compliance from adverse events or sub-optimal virological response, we excluded such patients. Indeed, Lim *et al*. [23] did not show also the statistical significance between the two groups ($p = 0.14$). Nevertheless, it is noteworthy that their Kaplan-Meier curves of the two groups did not cross each other during the whole follow-up period, [23] suggesting a possibility of positive results in a future study with a larger sample size and longer follow-up. One of the most plausible hypotheses explaining such a trend of the favorable outcome in patients treated with TAF is that they are more likely to achieve the

normalization of ALT than those receiving ETV or TDF, [10, 21, 22] given that on-treatment ALT normalization is associated with a lower risk of HCC development. [31–33] However, since the upper limit of normal value varies among studies and/or local laboratories and the ALT normalization itself is closely associated with various factors such as age, gender, steatosis, metabolic syndrome, alcohol use, and other medications that can potentially affect the long-term prognosis, further studies are required to draw a thorough conclusion. The carcinogenic potential of ETV and the induction of interferon (IFN)-λ3 production by tenofovir might in part explain the favorable outcome by TAF in comparison with ETV. However, such hypotheses are also still problematic. First, ETV was reported to increase the incidence of lung adenomas and carcinomas, HCC, and vascular tumors in mice at 4 mg/kg; and of HCC, brain microglial tumors, and skin fibroma in rats at 1.4–2.6 mg/kg. [34] However, these dosages are at least 100fold higher than those used in humans. In contrast, two recent large-scale real-life studies reported that long-term ETV therapy does not increase the risk of cancer. [35, 36] Moreover, in the long-term follow-up study by Kim *et al*. [37], the incidence of HCC was statistically not different during and after the first 5 years of ETV treatment (2.29% *vs*. 1.66%, $p = 0.22$). If long-term ETV maintenance retained significant pro-carcinogenic effects for humans, the HCC incidence would have progressed rapidly with time. In addition, although IFN-λ3 production might be induced by long-term TDF therapy, [27] conflicting data have also been reported. [28, 38–41] Because IFN-λ assays have not been standardized, neither its anti-carcinogenic effect in the human liver nor the causality of the relationship between higher IFN-λ3 levels and lower incidence of HCC has been confirmed.

This study also had some limitations. First, since TAF has been officially reimbursed by the National Health Insurance Service in the Republic of Korea since November 2017, a relatively small proportion of patients treated with TAF was available, and their follow-up data was not adequate to observe a sufficient number of liver-related events, which may introduce selection bias, particularly regarding treatment allocation. To overcome this, various statistical adjustments were performed, as well as subgroup analyses, which confirmed the reproducibility of the results. Nevertheless, a prospective cohort study of the association between antiviral type and HCC risk with long-term follow-up is needed. Second, most of our study population (> 98%) was infected with HBV genotype C through vertical transmission, which was significantly associated with the increased probability of HCC occurrence. [42–45] Thus, our results may not be representative of the full spectrum of the CHB population. However, given that the overall virological response rates by oral NUCs are similar across various HBV genotypes in contrast to pegylated interferon therapy, [42] it is possible that the present results would be largely maintained in different study populations. Lastly, the use of new biomarkers (e.g. serum quantitative HBsAg, serum hepatitis B core-related antigen, serum HBV-RNA, or specific HBV mutants) that could reflect the clinical course of CHB would have allowed more detailed analyses. [46–51]

In conclusion, the overall prognosis regarding HCC development was not statistically different between patients treated with ETV or TAF. Because prevention of liver-disease progression by appropriate antiviral therapy is a very important medical and socio-economical issue, further studies with long-term follow-up are needed to validate these results.

List Of Abbreviations

HBV, hepatitis B virus; CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; NUC, nucleos(t)ide analogue; ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; HR, hazard ratio; PS, propensity scores; HBeAg, hepatitis B e-antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; IPTW, inverse probability of treatment weighting.

Declarations

- Data Availability: Yes
- Animal Research (Ethics): N/A
- Consent to Participate (Ethics): N/A
- Consent to Publish (Ethics): N/A
- Plant Reproducibility: N/A
- Clinical Trials Registration: N/A
- Author Contribution: All authors conceived and designed the study. HL conducted statistical analyses, and all authors interpreted the findings. HWL, YYC, BKK, and SYP drafted the manuscript. HL, JSL, SUK, JYP, DYK and SHA critically reviewed the manuscript for key intellectual content. All authors approved the final manuscript. HCK and SUK are the guarantors, and as such, had full access to the data and take responsibility for its integrity and accuracy.
- Conflict of Interest: No
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Tables

Table 1. Comparison of baseline characteristics between two groups among the entire population				
Variables	**Total**	**ETV group**	**TAF group**	**p-value**
	(N=1810)	**(N=1525)**	**(N=285)**	
Age, years	52.8 ± 11.3	52.3 ± 11.4	49.5 ± 11.4	<0.001
Male, no. (%)	1085 (59.9)	915 (60.0)	170 (59.6)	0.912
Diabetes	301 (16.6)	274 (18.0)	27 (9.5)	<0.001
Hypertension	403 (22.3)	356 (23.3)	47 (16.5)	0.011
Liver cirrhosis	539 (29.8)	443 (29.0)	96 (33.7)	0.116
HBeAg positivity	685 (37.8)	523 (34.3)	162 (56.8)	<0.001
AST, IU/mL	75 ± 133.6	76.4 ± 131.8	83.8 ± 121.7	<0.001
ALT, IU/mL	80.5 ± 165.6	84.4 ± 165.7	105.1 ± 165.3	<0.001
Total bilirubin, mg/dL	1.1 ± 1.9	1.1 ± 1.9	1.0 ± 1.5	<0.001
Albumin, g/dL	4 ± 0.6	4.0 ± 0.6	4.1 ± 0.5	<0.001
Platelet count, ´ 10^3/mL	178.8 ± 81.3	178.9 ± 78.6	179.4 ± 62.9	<0.001

Data were reported as mean ± standard deviation or no. (%).
Abbreviations: ETV, entecavir; TAF, tenofovir alafenamie; HBeAg, hepatitis B e antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase

Table 2. Risk factors for the development of hepatocellular carcinoma

Variables	Univariate analysis	Multivariate analysis		
	P-value	Adjusted HR	95% CI	P-value
Male	<0.001	3.796	2.159~6.674	<0.001
Diabetes	0.049	0.831	0.491~1.407	0.491
Hypertension	<0.001	3.042	1.935~4.783	<0.001
Liver cirrhosis	0.003	1.801	1.184~2.739	0.006
HBeAg positivity	0.931	-	-	-
FIB-4 index	<0.001	1.084	1.029~1.142	0.002
Total bilirubin, mg/dL	0.438	-	-	-
Albumin, g/dL	0.018	0.954	0.633~1.438	0.823
TAF group (vs. ETV group)	0.255	-	-	-

Abbreviations: HR, hazard ratio; CI, confidence interval; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TAF, tenofovir alafenamide; ETV, entecavir

Table 3. Comparison of baseline characteristics between two groups after PS matching				
Variables	**Total**	**ETV group**	**TAF group**	**p-value**
	(N=570)	**(N=285)**	**(N=285)**	
Age, years	50.7 ± 11.2	50.1 ± 11.3	49.5 ± 11.4	0.304
Male, no. (%)	336 (58.9)	166 (58.2)	170 (59.6)	0.733
Diabetes	51 (8.9)	24 (8.4)	27 (9.5)	0.660
Hypertension	85 (14.9)	38 (13.3)	47 (16.5)	0.290
Liver cirrhosis	197 (34.6)	101 (35.4)	96 (33.7)	0.660
HBeAg positivity	321 (56.3)	159 (55.8)	162 (56.8)	0.800
AST, IU/mL	82.4 ± 152.4	83.1 ± 137.8	83.8 ± 121.7	<0.001
ALT, IU/mL	103.9 ± 208.7	104.5 ± 188.1	105.1 ± 165.3	<0.001
Total bilirubin, mg/dL	0.9 ± 0.8	1 ± 1.2	1 ± 1.5	0.187
Albumin, g/dL	4.1 ± 0.5	4.1 ± 0.5	4.1 ± 0.5	0.877
Platelet count, ´ 10^3/mL	170.5 ± 68.1	174.9 ± 65.6	179.4 ± 62.9	0.028

Data were reported as mean ± standard deviation or no. (%).
Abbreviations: PS, propensity score; ETV, entecavir; TAF, tenofovir alafenamie; HBeAg, hepatitis B e antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase

Table 4. Comparison of baseline characteristics between two groups after ITPW				
Variables	**Total**	**ETV group**	**TAF group**	**p-value**
Age, years	52.8 ± 11.3	52.8 ± 14.1	52.9 ± 24.1	<0.001
Male, no. (%)	1780.6 (58.9)	915 (60)	865.6 (57.8)	0.226
Diabetes	546.8 (18.1)	274 (18)	272.8 (18.2)	0.853
Hypertension	718.8 (23.8)	356 (23.3)	362.8 (24.2)	0.564
Liver cirrhosis	931.1 (30.8)	443 (29)	488.1 (32.6)	0.034
HBeAg positivity	1037.5 (34.3)	523 (34.3)	514.5 (34.4)	0.962
AST, IU/mL	75 ± 133.6	81.5 ± 164.4	88.2 ± 275.7	<0.001
ALT, IU/mL	80.5 ± 165.6	90.6 ± 209.6	100.9 ± 362.8	<0.001
Total bilirubin, mg/dL	1.1 ± 1.9	1.1 ± 2.4	1.1 ± 4.2	0.040
Albumin, g/dL	4 ± 0.6	4 ± 0.7	4 ± 1.2	0.001
Platelet count, ´ 10^3/mL	178.8 ± 81.3	175.2 ± 95	171.6 ± 148.2	0.220

Data were reported as mean ± standard deviation or no. (%).
Abbreviations: IPTW, inverse probability of treatment weighting; ETV, entecavir; TAF, tenofovir alafenamie; HBeAg, hepatitis B e antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase

Figures

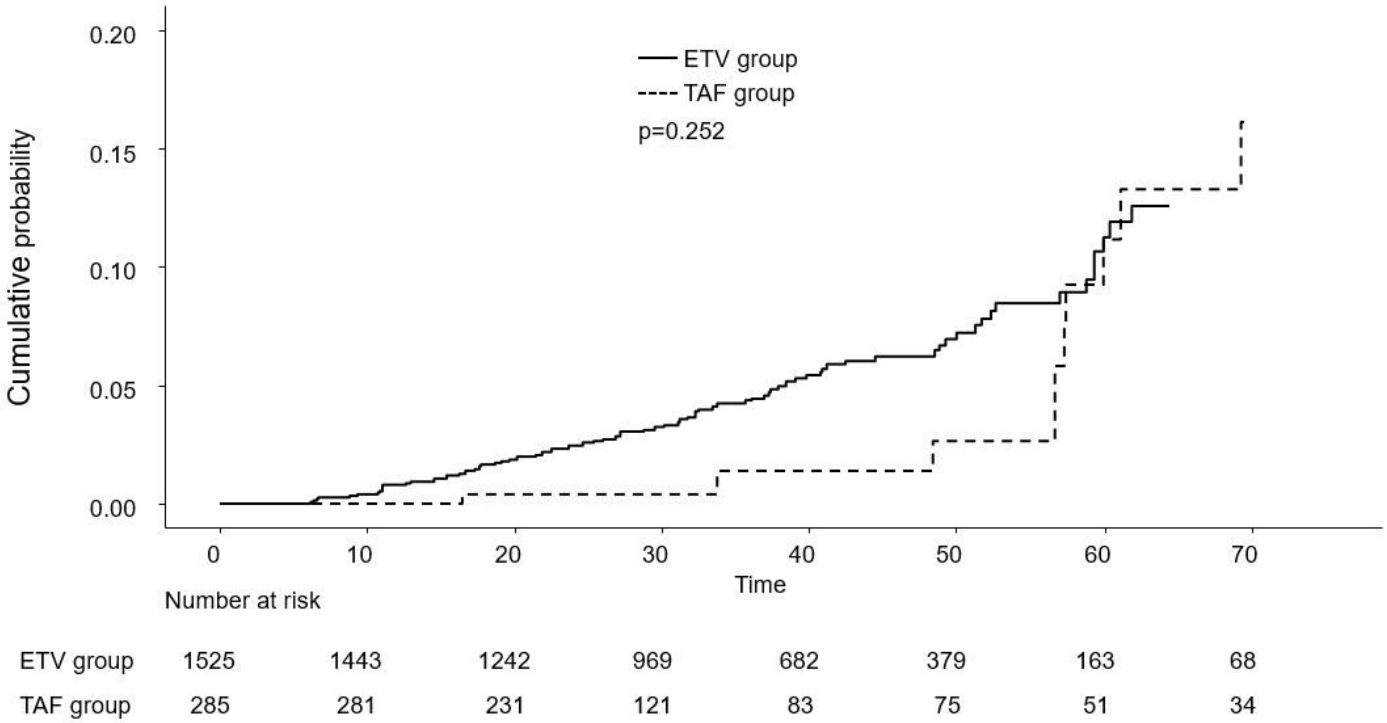

Figure 1

Kaplan-Meier curves of hepatocellular carcinoma (HCC) development between the two groups

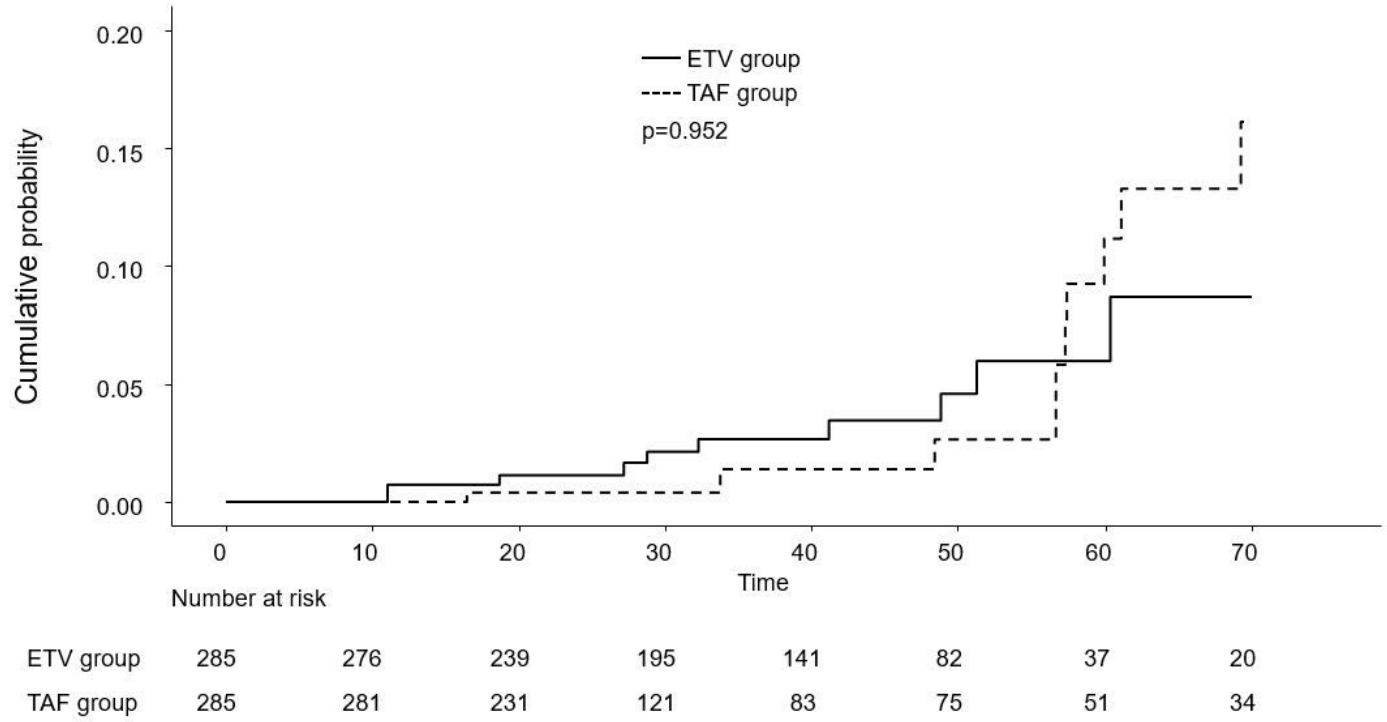

Figure 2

Kaplan-Meier curves of hepatocellular carcinoma (HCC) development between the two groups after 1:1 propensity score-matching analysis.

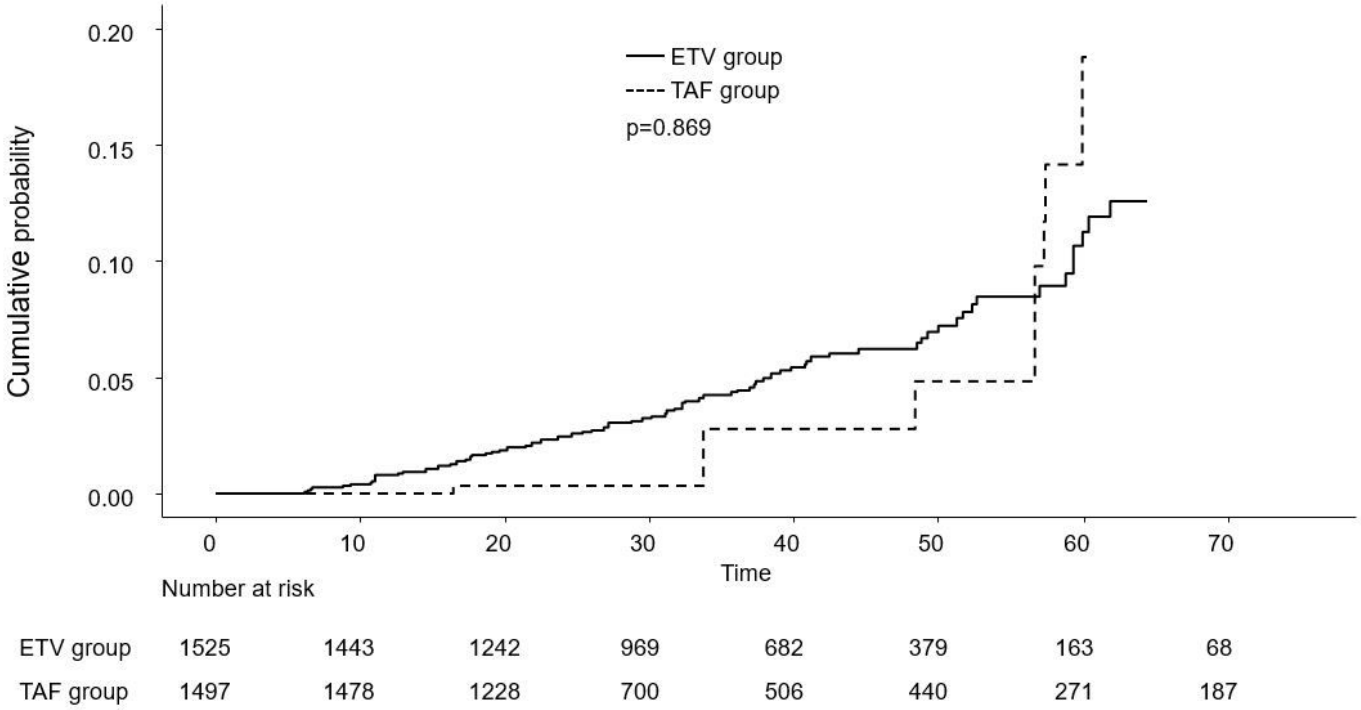

Figure 3

Kaplan-Meier curves of hepatocellular carcinoma (HCC) development between the two groups after inverse probability of treatment weighting analysis.

Supplementary Files

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