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Meta-analysis of the occurrence of hepatocellular carcinoma after the treatment of entecavir and tenofovir for chronic hepatitis B

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Abstract

Background: Tenofovir and Entecavir are recommended as the first-line medicine of treatment for chronic hepatitis B. The occurrence of hepatocellular carcinoma after the treatment of chronic hepatitis B is a major problem. For the time being it is still unclear whether there remains a difference in risk correlation of hepatocellular carcinoma after the treatment of Tenofovir and Entecavir for chronic hepatitis B. Since previous studies have raised different ideas, this article aims to come to a conclusion targeting such a topic through analyzing the latest data.

Methods: We searched some databases, such as PubMed, Web of Science, and Cochrane Library, for related studies on patients with chronic hepatitis B receiving the treatment of Tenofovir and Entecavir and then developing hepatocellular carcinoma. The search time was set to begin from the establishment time of the above-mentioned databases to May 2022. Two researchers were designated to screen the literature independently according to the inclusion and exclusion criteria set in this study; they then evaluated the quality of the literature included and extracted the data. Revman 5.3 software was used for meta-analysis.

Results: After screening the literature, a total of 20 pieces of cohort study literature conformed to the inclusion criteria. Among which were 62,860 cases of patients receiving Entecavir, and 27,544 cases of patients receiving Tenofovir; there were 3669 cases with the occurrence of hepatocellular carcinoma in the Entecavir group and 1089 cases with the occurrence of hepatocellular carcinoma in Tenofovir group. The result of Meta analysis of these 20 pieces of literature shows that compared with the Tenofovir group, the Entecavir group has a lower occurrence rate of hepatocellular carcinoma, and the difference is statistically significant. The results are expressed as odd ratio (OR) and 95% confident interval (95%CI), (OR = 1.66, 95%CI: 1.35–2.05, P < .05). The result of Meta analysis of 10 studies related to Korea shows that the occurrence rate of hepatocellular carcinoma in the Tenofovir group is lower than that of the Entecavir group, and the difference is statistically significant (OR = 1.59, 95%CI: 1.29–1.95, P < .05). The result of meta-analysis of 5 studies related to China shows that the occurrence rate of hepatocellular carcinoma of Tenofovir group is lower than that of Entecavir group, and the difference is statistically significant (OR = 2.35, 95%CI: 1.15–4.81, P < .05).

Conclusion: The occurrence rate of hepatocellular carcinoma after the treatment of tenofovir for chronic hepatitis B is lower than that of the treatment of entecavir.

Abbreviations: CHB = chronic hepatitis B, 95%CI = 95% confident interval, ETV = entacavir, HBV = hepatitis B virus, HBVDNA = hepatitis B virus deoxyribonucleic acid, HCC = hepatocellular carcinoma, OR = odd ratio, TDF = tenofovir.

Keywords: entecavir, hepatocellular carcinoma, tenofovir

1. Introduction

The infection of the hepatitis B virus (HBV) is still a global public health issue. Although the widely-available vaccine inoculation program has reduced the load of liver disease in the population, now there is no certain method to fully eliminate this virus. Hepatocellular carcinoma (HCC) is the most common primary liver cancer, and its incidence ranks 6th among all malignant tumors. The infection of HBV is an important risk factor for developing hepatocellular carcinoma. Patients with chronic hepatitis B have an increasing potential of developing hepatic sclerosis and HCC. Antiviral treatment can prevent the development of disease, raise the quality of life and living, and reduce the incidence of HCC. Preventing the occurrence of HCC is still the major problem of treatment for patients with chronic hepatitis B. The long-term suppression of the replication of HBV is a major endpoint of today therapeutic strategy, while the loss of HBsAg is the

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The datasets generated during and/or analyzed during the current study are publicly available.

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best endpoint. Being nucleoside analogues with high antiviral effect and strong drug resistance barrier, tenofovir (TDF), and entacavir (ETV) are the first-line medicine for treating the infection of HBV.[1,2] Although hepatitis B virus deoxyribonucleic acid (HBVDNA) is not detected in serum when using the nucleoside analogues in the antiviral treatment, HCC can still occur. Even though ETV and TDF can reduce the risk of the occurrence of HCC, the previous studies and Meta analyses show the contradiction when comparing the reduction of the risk of HCC by 2 drugs. Recently, the comparison of the effect of 2 drugs on reducing the risk of HCC provokes people great interest. Two large-scale observation reports from Asia show that the risk of HCC in the patients receiving TDF treatment is obviously lower than those receiving ETV treatment, so TDF is associated with the reduction of HCC risk.[3,4] However, this is inconsistent with the results of another 2 large-scale studies which show no significant difference of the reduction of HCC risk between the 2 drugs.[5,6]

Our purpose is to compare the effect of ETV and TDF on reducing the risk of HCC by including the recent high-quality studies and to analyze the heterogeneity between studies through the subgroup analysis to help clinicians decide on proper treatments.

2. Material and Methods

2.1. Subject

Based on the predetermined search strategy (search range, search terms, search time), the related literature on ETV and TDF treating chronic hepatitis B was searched on the computer, and the clinical trials complied with the inclusion criteria were chosen as the subjects.

3. Methods

3.1. Inclusion criteria

Subject: patients without HCC and not yet received the antiviral treatment for chronic hepatitis B; intervention measures: single drug ETV or single drug TDF; study type: random control trial or cohort study; the results of the study: the occurrence of HCC.

3.2. Exclusion criteria

The patients complicating other viral hepatitis; the studies applying or co-applying other antiviral drugs; the patients had suffered HCC in the past; literature of duplicate publication; the original material and base is not complete.

3.3. Search strategy

Search in the databases of PubMed, Web of Science, and Cochrane Library for related studies on the occurrence of HCC after the treatment of single drug TDF and ETV in patients with chronic hepatitis B. The search time was set from the establishment time of the above-mentioned databases to May 2022. The search terms include Chronic hepatitis B, Hepatocellular carcinoma, entecavir, and tenofovir.

3.4. Evaluation method

Two researchers were designated to screen the literature independently according to the inclusion and exclusion criteria set in this study, then evaluated the quality of included literature and extracted and filled the data into the pre-designed tables. If the 2 researchers have different ideas in the process of screening literature, a third researcher will make the judgement. The following contents are extracted from the literature: the general information of the study: the author name, year of publication, the region/nation of the research, the patient age, the patient gender, the type of study, and follow-up time. characteristics of study: sample size and the condition of hepatocirrhosis. the index of outcome: the occurrence of HCC. The evaluation of the quality of literature is based on the random control experiment tool in Cochrane coordination web and Newcastle-Ottawa scale for cohort study. The evaluation criteria include the chosen population, comparability between groups, and the measurement of results; the full mark is 9, ≥6 mark represents high quality, <6 mark represents low quality. The evaluation of the literature was done by 2 researchers independently. If different ideas occur, the 2 researchers will either discuss and reach an agreement or a third person will make a judgment.

4. Statistical analysis

This Meta analysis chose the RevMan5.3 software provided by Cochrane coordination web to do the heterogeneity analysis between included studies, using the Q test and I^2 test. The more the value of I^2 is, the bigger the heterogeneity is. If the result of heterogeneity analysis between included studies is $P > .1$, it is considered that homogeneity exists between studies, then the fix effect model analysis should be adopted. If $P \leq .1$, it shows that heterogeneity exists between studies, the source of heterogeneity should be analyzed first, then the subgroup analysis or sensitivity analysis should be conducted on the factors that may cause heterogeneity, such as age, gender, and the patients' conditions; once the above factors had reached homogeneity, the fix effect model was used. If the analysis was conducted yet the result remained heterogeneity, then the random effect model will be used to do the meta-analysis. Generally, I^2 is used to quantitatively estimate the heterogeneity, if $I^2 = 0$ represents no heterogeneity exists between studies, when $I^2 < 25\%$, the heterogeneity between studies is relatively low, $25\% \leq I^2 \leq 50\%$ represents moderate heterogeneity, and $I^2 > 50\%$ can be considered as high heterogeneity between studies. Meta analysis needs to merge the results of multiple studies of the same kind into a single effect-size or effect magnitude, which means a particular merged statistic size would reflect the comprehensive effect of multiple studies of the same kind. In this study, binary data was analyzed with meta-analysis, using odd ratio (OR) and 95% confident interval (95%CI) to represent, and the test result was obtained with a forest plot.

5. Results

5.1. The result of the search for literature

Based on the search strategy set in this study, a total of 2258 pieces of literature related to Entecavir and Tenofovir treating chronic hepatitis B were retrieved through the preliminary search. After the exclusion of the duplicated and unrelated literature, 1165 pieces of literature still remain. By reading the title and abstract first and with the help of the preliminary judgment, a total of 617 pieces of literature were excluded for not being consistent with the inclusion criteria. After reading the full text of the remaining 48 pieces of literature, a total of 20 pieces of literature were included.[3–22] The search, screening flow path, and results are depicted in Figure 1.

5.2. The basic characteristics and quality evaluation of the research literature included

The 20 pieces of research literature included are all cohort studies, among which are 62,860 cases in the ETV group and 27,544 cases in the TDF group. There are 3649 cases with the occurrence of HCC in the ETV group, and 1086 cases with the occurrence of HCC in the TDF group. For all the literature,

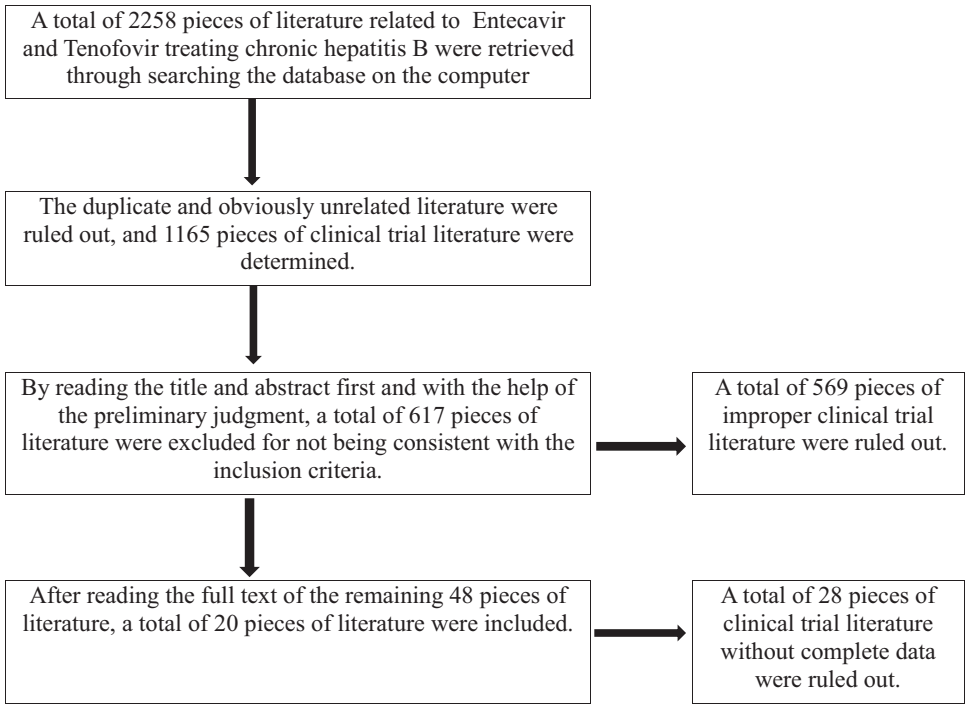

Figure 1. Flow chart of literature-search.

Newcastle-Ottawa scale ≥ 7 marks. The basic characteristics of the research literature included studies were detailed in **Table 1**.

5.3. The result of meta-analysis

A heterogeneity test was conducted in the 20 studies and the results show that heterogeneity exists between studies ($P < .1$, $I^2 = 80\%$), thus the source of heterogeneity was analyzed and a subgroup analysis was conducted on the factors that may cause heterogeneity. Further analysis shows that heterogeneity originates from the study in 2018 by Yip etc (weight 1.3%). After removing that study, the result shows that the heterogeneity lowers ($P < .1$, $I^2 = 74\%$), but the heterogeneity still exists. The random-effect model was used to analyze the incidence of HCC. Compared with the ETV group, the incidence of HCC was lower than that of the ETV group and the difference is statistically significant (OR = 1.68, 95%CI: 1.37–2.07, $P < .05$). See Figure 2.

To eliminate the influences of different nations and regions, 10 out of 20 pieces of literature involved studies conducted in Korea. The result of the heterogeneity test between studies shows that heterogeneity exists between studies ($P < .1$, $I^2 = 62\%$) and the random-effect model was adopted to analyze the HCC incidence. The results of Meta analysis show that compared with the ETV group, the TDF group has a lower incidence of HCC and the difference is statistically significant (OR = 1.59, 95%CI: 1.29–1.95, $P < .05$). The further analysis shows that the heterogeneity originates from the study in 2020 by Ha etc (weight 0.7%) and the study in 2020 by Oh etc (weight 6.2%). After removing these 2 studies, the result shows that ($P > .1$, $I^2 = 25\%$), the heterogeneity was eliminated and the incidence of HCC in the TDF group is lower than that of the ETV group, and the difference is statistically significant (OR = 1.66, 95%CI: 1.50–1.84, $P < .05$). See Figure 3. 5 out of 20 studies were related to China, and the results of the heterogeneity test between studies show that heterogeneity exists in different studies ($P < .1$, $I^2 = 89\%$), and further analysis shows that the heterogeneity originates from the study in 2019 by Yip, etc (weight 6.8%). After removing the study, the result shows ($P < .1$, $I^2 = 77\%$) that the heterogeneity still exists. Then the random-effect model was adopted to analyze the incidence of HCC. The results of meta-analysis show that compared with the ETV group, the TDF group has a lower incidence of HCC and the difference is statistically significant (OR = 2.35, 95%CI: 1.15–4.81, $P < .05$). See Figure 4.

5.4. The sensitivity analysis and bias

To conduct the meta-analysis, we eliminated the single study in turn, so that the total effect size would not be influenced by the single study, and the results of meta-analysis will be steady. The funnel plot was used to evaluate the bias, and the symmetrical invert "funnel" indicates no bias.

6. Discussion

The world health organization evaluated in 2019 that about 296 million people having chronic hepatitis B in the world, and around 820 people died of liver cancer or hepatocirrhosis; such incidence had been increasing.[23] Liver cancer is still a global health challenge. As estimated, there will be 1 million people affected by liver cancer by 2025. HCC is the most common form of liver cancer, accounting for about 90%. Among which the infection of HBV is the most important risk factor for the occurrence of HCC, accounting for about 50% of the HCC.[24] The risk factor of HCC in patients with chronic hepatitis B (CHB)is often related to the host, virus, and environment or lifestyle. HCC occurs differently in the vertically-propagating cousins with the same HBV viral genotype. The factor of the host includes age, male, hepatocirrhosis, the familial history of liver cancer, diabetes, and metabolic syndrome. The vital factor includes HBeAg positive, HBsAg quantity, HBVDNA level, and HBV genotype. The factors related to environment or lifestyle include drinking and exposure to aflatoxin.[25–27]

HBV is a kind of DNA virus that belongs to the hepatovirus family and has a unique republication process and pathogenesis. Inside the cell, the DNA of the virus first transforms into RNA and then reversely transcripts into DNA. Chronic HBV infection

Table 1

The general characteristics of the included literatures.

The included literature (author, yr of publication, nation)	Study design	Sample size		Gender (Male)		Age (yr)		Follow-up time (mo)		Hepatocirrhosis		HCC	
		ETV	TDF	ETV	TDF	ETV	TDF	ETV	TDF	ETV	TDF	ETV	TDF
Guzellbulut et al,[9] 2021, Turkey	Retrospective study	248	359	178	219	45.54 ± 13.69	43.69 ± 13.22	58.58 ± 37.9	46.96 ± 29.37	89	76	12	7
Yip et al,[4] 2019, Taiwan, China	Retrospective study	28041	1309	18094	591	53.4 ± 13.0	43.2 ± 13.1	3.7 (1.7–5.0)	2.8 (1.4–4.5)	3822	38	1386	8
Choi et al,[3] 2018, Korea	Retrospective study	11464	12692	unknown	unknown	49.3	48.6	unknown	unknown	2991	3488	590	394
Ha I et al,[10] 2020, Korea	Retrospective study	921	419	558	266	48	45	unknown	unknown	259	39	82	24
Hsu et al,[12] 2018, Taiwan, China	Prospective study	224	21	unknown	unknown	unknown	unknown	unknown	unknown	unknown	unknown	20	0
Hsu et al,[5] 2019, multiple centers	Prospective study	4837	700	3382	465	50.81 ± 0, 17	45.74 ± 0.47	unknown	unknown	unknown	unknown	285	13
Kim et al,[6] 2019, Korea	Retrospective study	1484	1413	unknown	unknown	48.2	48.8	unknown	unknown	499	411	138	102
Lee et al,[14] 2019, Korea	Retrospective study	1583	1439	841	926	46.66	47.29	51.5	36.4	567	483	84	50
Oh et al,[16] 2020, Korea	Retrospective study	753	807	480	503	48.7 ± 11.4	46.3 ± 11.2	4.7 ± 1.0	4.5 ± 1.1	315	310	34	45
Shin et al,[19] 2020, Korea	Retrospective study	894	900	597	571	52 ± 11	51 ± 11	72	72	440	375	74	31
Wu et al,[21] 2017, China	Retrospective study	313	106	230	74	47 ± 12.3	47.1 ± 12.1	49.1 ± 19.1	37.9 ± 7.2	94	29	21	8
Yu et al,[22] 2018, Korea	Retrospective study	406	176	272	104	18–84	20–84	6–119.4	6.3–119.4	148	77	31	7
Chang et al,[7] 2021, Taiwan, China	Retrospective study	5348	1900	3544	1302	54 ± 11.9	51 ± 12.2	39.6 ± 24.6	40.1 ± 22.1	1590	590	375	100
Chen et al,[8] 2020, Taiwan, China	Retrospective study	993	567	721	428	55.4 ± 11.7	54.5 ± 12.9	65.8	47.7	993	567	196	48
Ha et al,[10] 2020, Korea	Retrospective study	180	224	106	120	45.4 ± 10.8	44.5 ± 11.4	64	49.1	67	78	18	6
Kim et al,[13] 2018, Korea	Retrospective study	721	604	471	363	52 ± 11	50 ± 11	33	66	346	267	40	14
Papatheodoridis et al,[17]2020, multiple nations	Retrospective study	772	1163	538	827	52 ± 14	53 ± 13	51.6–114.0	64.8–115.2	166	358	50	93
Pol et al,[18] 2021, France	Prospective study	814	986	597	666	39.7–58.9	35.0–56.5	37.1–60.7	37.1–60.7	69	90	9	12
Su et al,[20] 2020, US	Retrospective study	2193	1094	2116	1039	56.5 ± 12.2	55.4 ± 12.4	67.2	56.4	453	228	167	85
Na et al,[15] 2021, Korea	Retrospective study	671	665	392	384	44–57	42–56	62.4	45.6	377	302	57	42

ETV = entecavir, HCC = hepatocellular carcinoma, TDF = tenofovir.

is a dynamic process in which the immune response happens between HBV and the hepatic cells of the host. The republication of active HBV is a key driving factor that causes the necrosis of hepatic cells and the development of disease. With the republication of the virus, the immune system begins to make responses that cause damage to hepatic cells. That means the virus itself doesn't lead to the damage of the hepatic cells. Now ETV and TDF can only inhibit the replication of the virus, but can not fully eliminate it; that is to say, it is possible to clear the covalently closed circular DNA, yet hard to fulfill the functional cure, which means the loss of HBsAg.[23,28,29]

A report from Hong Kong involves 222 cases of patients with CHB who receive primary treatment. These patients have received a 5-year treatment of ETV, and the result shows that HBVDNA can't be detected in 97.1% of the patients (<20 IU/mL), the serological conversion of HBeAg is fulfilled in 66.9% of the patients, HBsAg disappears in 1 case, and the 5-year cumulative drug resistance rate is 1.2%.[30] Another study shows that after the patients with CHB had received a 7-year treatment of TDF, HBVDNA is not detected in 99.3% of the patients, HBeAg disappears in 55.4% of the patients, and HBsAg disappears in 11.8% of the patients.[31] In a study that the patients with the infection of HBV who receive the treatment of TDF, the drug resistance against TDF is not found until the tenth year.[32] ETV and TDF are recommended as the first-line medicine treatment for CHB because of their high efficacy in inhibiting the replication of HBVDNA and safety. Long-term antiviral treatment is usually necessary. The benefits of antiviral treatment for patients with CHB include long-term inhibition of the replication of the virus and reducing the hepatic fibrosis, even inverting the hepatocirrhosis to reduce the risk of the occurrence of HCC.

This meta-analysis has some limitations. The age, conditions, region, and the compliance of the included patients are varied, which might influence the reliability of the results. After

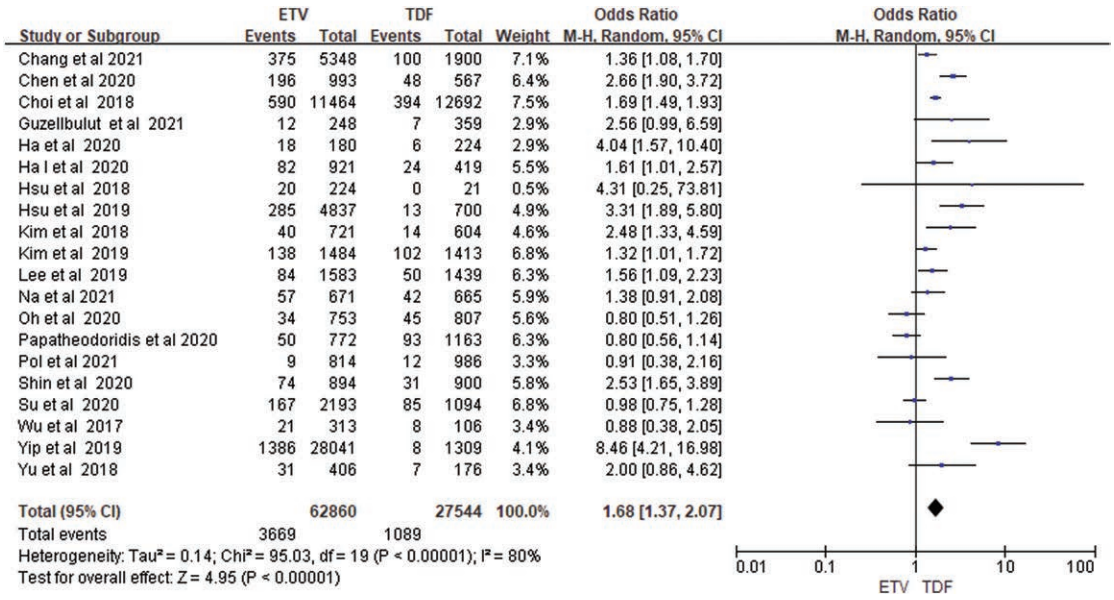

Figure 2. The comparison of the HCC incidence between the ETV and TDF groups. ETV = entecavir, HCC = hepatocellular carcinoma, TDF = tenofovir.

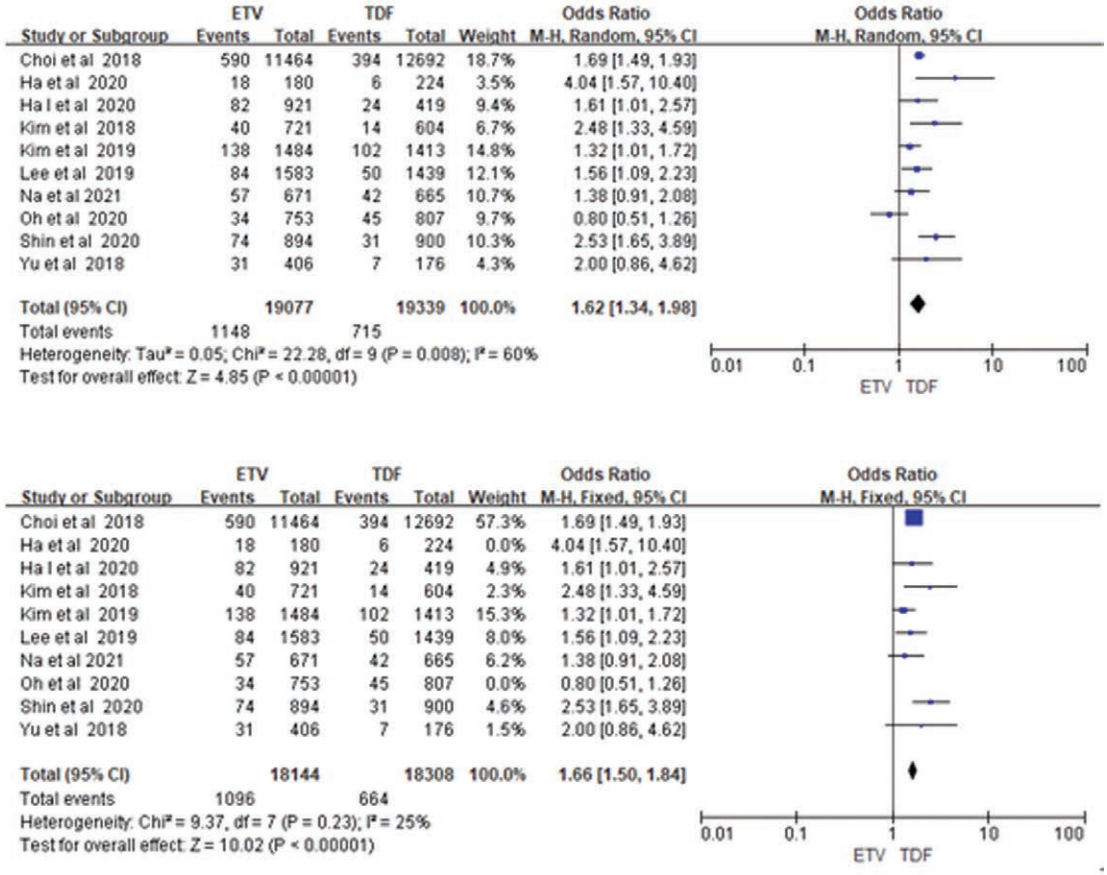

Figure 3. The comparison of the HCC incidence between the ETV and TDF group in the studies related to Korea. ETV = entecavir, HCC = hepatocellular carcinoma, TDF = tenofovir.

observing the general characteristics of the literature, we found that the age (the patients in the ETV group are older than that of the TDF group) and follow-up time (the follow-up time of ETV is longer than that of the TDF group) of ETV group and TDF group are both different. In clinical practice, clinicians will prescribe ETV to patients with kidney damage or chronic diseases related to kidney diseases, and will preferentially prescribe ETV to patients with severe liver disease when they consider that long-term use of TDF is associated with kidney damage,[33] resulting in the younger age of patients in the TDF group, their liver disease is milder, and they have no kidney-related disease, which is in favor of TDF to reduce the risk of HCC. Besides, as

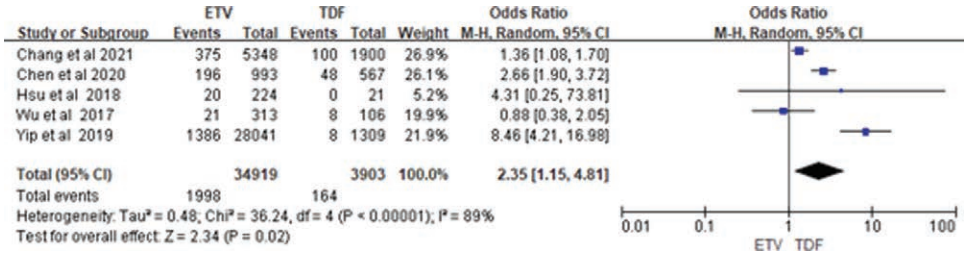

Figure 4. The comparison of the HCC incidence between the ETV and TDF group in the studies related to China. ETV = entecavir, HCC = hepatocellular carcinoma, TDF = tenofovir.

the viral factor of the risk of HCC, HBV genotyping, especially gene C typing, owns a higher risk of HCC, but the included studies in this meta-analysis do not mention such an issue. The result of this meta-analysis is different from the results of several previous studies, so further larger-scale study is needed to make clear whether there is a difference in reducing the risk of HCC between the ETV group and the TDF group. Maintaining a complete or constant viral response is crucially important for the prevention of HCC. At present, the 2 antiviral drugs are both suitable for clinical practice.

Many other studies find that 20% to 40% of the patients who receive long-term antiviral treatment of ETV and TDF are still in a low level of viremia, that is < 2000 IU/mL. A low level of viremia is an independent risk factor for HCC, especially the patients with hepatocirrhosis accompanying low viremia, the risk of HCC increases when the clinicians should consider adjusting the therapeutic regime.[34] Otherwise, the occurrence of HCC is also possible in the immune tolerance, so looking for a proper beginning, and end of antiviral treatment and launching antiviral treatment in the early stage will be a better strategy, which can reduce the risk of HCC in patients in the gray zone; however, more clinical research evidence is needed to reach this goal.[35]

We need to keep trying to determine patients with the infection of HBV through targeting screening to prevent the new infection by active inoculating the hepatitis B vaccine, and actively monitoring and treating the hepatitis patients with the indication of treatment, including monitoring HCC. With the intensive study of pathogenesis and molecular biology of the hepatitis B virus, many new therapeutic methods are actively developed, and the final aim is to develop a kind of safe, effective, well-tolerant therapeutic regime with limited treatment duration to achieve the goal of eliminating viral hepatitis, a major public health threaten, by 2030 launched by world health organization to reduce the occurrence of HCC.[36]

7. Conclusions

The meta-analysis was used to analyze the incidence of HCC that occurred after the treatment of ETV and TDF for the patients with CHB, and the result shows that the incidence of HCC of the patients with CHB in the TDF group is lower than that of the ETV group, and the difference is statistically significant (OR = 1.66, 95%CI: 1.35–2.05, $P < .05$). After the subgroup analysis was conducted based on different nations and regions, the incidence of HCC in the TDF group is lower compared with that in the ETV group, and the difference is statistically significant.

Author contributions

Data curation: Kaiyue Tang, Yueping Guo.
Methodology: Haiyan Wang.
Visualization: Yueping Guo.
Writing – original draft: Kaiyue Tang.
Writing – review & editing: Huizhen Cheng.

References

[1] European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. Clin Pract Guidel. 2017;67:370–98.
[2] Wang G, Duan Z. Guidelines for prevention and treatment of chronic hepatitis B. J Clin Transl Hepatol. 2021;9:769–91.
[3] Choi J, Kim HJ, Lee J, et al. Risk of hepatocellular carcinoma in patients treated with entecavir vs tenofovir for chronic hepatitis B: a Korean nationwide cohort study. JAMA Oncol. 2019;5:30–6.
[4] Yip TC-F, Wong VW-S, Chan HL-Y, et al. Tenofovir is associated with lower risk of hepatocellular carcinoma than entecavir in patients with chronic HBV infection in China. Gastroenterology. 2020;158:215–225.e6.
[5] Hsu Y-C, Wong GL-H, Chen C-H, et al. Tenofovir versus entecavir for hepatocellular carcinoma prevention in an international consortium of chronic hepatitis B. Am J Gastroenterol. 2020;115:271–80.
[6] Kim SU, Seo YS, Lee HA, et al. A multicenter study of entecavir vs. tenofovir on prognosis of treatment-naïve chronic hepatitis B in South Korea. J Hepatol. 2019;71:456–64.
[7] Chang T-S, Yang Y-H, Chen W-M, et al. Long-term risk of primary liver cancers in entecavir versus tenofovir treatment for chronic hepatitis B. Sci Rep. 2021;11:1365.
[8] Chen C-H, Chen C-Y, Wang J-H, et al. Comparison of incidence of hepatocellular carcinoma between chronic hepatitis B patients with cirrhosis treated with entecavir or tenofovir in Taiwan-a retrospective study. Am J Cancer Res. 2020;10:3882–95.
[9] Güzelbulut F, Gökçen P, Can G, et al. Comparison of the efficacy of entecavir and tenofovir in reducing hepatocellular carcinoma risk in chronic hepatitis B patients: a real-life study in Turkey. Turk J Gastroenterol. 2021;32:412.
[10] Ha I, Chung JW, Jang ES, et al. Comparison of the on-treatment risks for hepatocellular carcinoma between entecavir and tenofovir: a propensity score matching analysis. J Gastroenterol Hepatol. 2020;35:1774–81.
[11] Ha Y, Chon YE, Kim MN, et al. Hepatocellular carcinoma and death and transplantation in chronic hepatitis B treated with entecavir or tenofovir disoproxil fumarate. Sci Rep. 2020;10:13537.
[12] Hsu Y-C, Jun T, Huang Y-T, et al. Serum M2BPGi level and risk of hepatocellular carcinoma after oral anti-viral therapy in patients with chronic hepatitis B. Aliment Pharmacol Ther. 2018;48:1128–37.
[13] Kim BG, Park NH, Lee SB, et al. Mortality, liver transplantation and hepatic complications in patients with treatment-naïve chronic hepatitis B treated with entecavir vs tenofovir. J Viral Hepatitis. 2018;25:1565–75.
[14] Lee SW, Kwon JH, Lee HL, 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;69:1301–8.
[15] Na JE, Sinn DH, Lee JH, et al. Efficacy of entecavir versus tenofovir in preventing hepatocellular carcinoma in patients with chronic hepatitis B with maintained virologic response. J Viral Hepatitis. 2021;28:1392–9.
[16] Oh H, Yoon EL, Jun DW, et al. No difference in incidence of hepatocellular carcinoma in patients with chronic hepatitis B virus infection treated with entecavir vs tenofovir. Clin Gastroenterol Hepatol. 2020;18:2793–2802.e6.
[17] Papatheodoridis GV, Dalekos GN, Idilman R, et al. Similar risk of hepatocellular carcinoma during long-term entecavir or tenofovir therapy in Caucasian patients with chronic hepatitis B. J Hepatol. 2020;73:1037–45.
[18] Pol S, Bonnet D, Payssan-Sicart V, et al. Similar 5-year HCC occurrence in tenofovir-and entecavir-treated HBV chronic infection in the French AFEF/ANRS CO22 Hepather cohort. Aliment Pharmacol Ther. 2021;53:616–29.

[19] Shin JW, Jeong J, Jung SW, et al. Comparable incidence of hepatocellular carcinoma in chronic hepatitis B patients treated with entecavir or tenofovir. Dig Dis Sci. 2021;66:1739–50.
[20] Su F, Berry K, Ioannou GN. No difference in hepatocellular carcinoma risk between chronic hepatitis B patients treated with entecavir versus tenofovir. Gut. 2021;70:370–8.
[21] Wu IT, Hu TH, Hung CH, et al. Comparison of the efficacy and safety of entecavir and tenofovir in nucleos(t)ide analogue-naive chronic hepatitis B patients with high viraemia: a retrospective cohort study. Clin Microbiol Infect. 2017;23:464–9.
[22] Yu JH, Jin Y-J, Lee J-W, et al. Remaining hepatocellular carcinoma risk in chronic hepatitis B patients receiving entecavir/tenofovir in South Korea. Hepatol Res. 2018;48:862–71.
[23] Noverati N, Bashir-Hamidu R, Halegoua-DeMarzio D, et al. Hepatitis B virus-associated hepatocellular carcinoma and chronic stress. Int J Mol Sci . 2022;23:3917.
[24] Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2021;7.
[25] Philips CA, Ahamed R, Abduljaleel JK, et al. Critical updates on chronic hepatitis B virus infection in 2021. Cureus. 2021;13:e19152.
[26] Roberts SK, Majeed A, Kemp W. Controversies in the management of hepatitis B: hepatocellular carcinoma. Clin Liver Dis. 2021;25:785–803.
[27] Wang S, Liu B, Fan X, et al. Predicting the risk of hepatocellular carcinoma in chronic hepatitis B patients receiving antiviral therapy: validating the CAMD and AASL scores in China. Saudi J Gastroenterol. 2022.
[28] Chien R-N, Liaw Y-F. Current trend in antiviral therapy for chronic hepatitis B. Viruses. 2022;14:434.
[29] Yardeni D, Ghany MG. Review article: hepatitis B—current and emerging therapies. Aliment Pharmacol Ther. 2022;55:805–19.
[30] Seto W-K, Lam Y-F, Fung J, et al. Changes of HBsAg and HBV DNA levels in Chinese chronic hepatitis B patients after 5 years of entecavir treatment. J Gastroenterol Hepatol. 2014;29:1028–34.
[31] Buti M, Tsai N, Petersen J, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. Dig Dis Sci. 2015;60:1457–64.
[32] Marcellin P, Wong DK, Sievert W, et al. Ten-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B virus infection. Liver Int. 2019;39:1868–75.
[33] Masetti C, Pugliese N, Aghemo A, et al. Safety of current antiviral drugs for chronic hepatitis B. Expert Opin Drug Saf. 2022:1–7.
[34] Zhang Q, Peng H, Liu X, et al. Chronic hepatitis B infection with low level viremia correlates with the progression of the liver disease. J Clin Transl Hepatol. 2021;9:850–9.
[35] Yoon EL, Jun DW. Precision medicine in the era of potent antiviral therapy for chronic hepatitis B. J Gastroenterol Hepatol. 2022;37:1191–6.
[36] Liu J, Liang W, Jing W, et al. Countdown to 2030: eliminating hepatitis B disease, China. Bull World Health Organ. 2019;97:230–8.