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Magnitude of and Prediction for Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Taking Entecavir or Tenofovir Therapy: A Systematic Review

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jgh.15078

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Funding source:

The study is supported by E-DA Hospital (EDCHP103046) , Tomorrow Medical Foundation (2019-TMF-P003), and National Institutes of Health grant P30 DK056338 (Study Design and Clinical Research Core), which supports the Texas Medical Center Digestive Diseases Center.

Author contributions statement

Data collection: Cheng-Hao Tseng, Chao-Ming Tseng, Yao-Chun Hsu, Jia-Ling Wu

Data analysis: Cheng-Hao Tseng, Chao-Ming Tseng , Yao-Chun Hsu, Jia-Ling Wu

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Data interpretation and critical review/revision of the manuscript: All authors

Study concept and study supervision: Yao-Chun Hsu, Hashem B. El-Serag

Conflict of interest :

HBE: HBE received research funding from Gilead and Merck. This work was supported in part by National Institutes of Health grant P30 DK056338 (Study Design and Clinical Research Core), which supports the Texas Medical Center Digestive Diseases Center.

YCH: YCH received research support from Gilead Sciences, and served as an advisory committee member for Gilead Sciences, and has been a speaker for Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, and Novartis.

CHT,CMT, JLW: None declared

ABSTRACT

Background & Aims: Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) have been shown to reduce incidence of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB). This systematic review aims to evaluate the magnitude, change over time, and prediction of residual HCC risks in CHB patients treated with ETV/TDF therapy.

Methods: Available literature was systematically reviewed through searches of PubMed and EMBASE databases from January 1, 2006, to September 1, 2019, to identify cohort studies that reported HCC incidence in CHB patients during ETV/TDF therapy. Studies were screened by title and abstract and then evaluated for eligibility in terms of full text.

Results: We identified 141 studies for full-text review, and 34 were eligible for analysis. From 19 studies with data separated by cirrhosis status, the 5-year cumulative incidence of HCC was 0.5~6.9% in patients without cirrhosis, 4.5~21.6% in compensated cirrhosis, and 36.3~46.5% in decompensated cirrhosis. All 4 studies that addressed temporal changes in HCC risks consistently found the incidence rate decreased over time in patients with cirrhosis, although the findings were inconsistent in patients without cirrhosis. Six predictive scores were developed and validated to predict incident HCC during ETV/TDF therapy in CHB patients. Common scoring variables included age, sex, cirrhosis (fibrosis grade) and hepatic function. Conflicting results were reported in 7 individual studies and 2 meta-analyses that compared ETV vs. TDF.

Conclusions: The residual risk of HCC remains during ETV/TDF treatment in CHB patients with cirrhosis, but declines over time. Risk stratification is attainable by validated predictive scores.

Key words: Hepatocellular carcinoma, Chronic hepatitis B infection, Entecavir, Tenofovir disoproxil fumarate.

INTRODUCTION

Hepatitis B virus (HBV) infection is a global health problem that affects approximately 240 million people around the world and leads to more than 686,000 deaths a year [1]. Hepatocellular carcinoma (HCC) is a major complication of chronic hepatitis B (CHB) virus infection, and natural history studies have shown that a high HBV viral load is associated with increased HCC risk [2]. Conversely, compelling evidence shows that long-term viral suppression with antiviral therapy can reduce the occurrence of HBV-related HCC [3]. For long-term treatment, entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide are the recommended first-line regimens according to current international guidelines [4-6].

Most studies have reported positive effects of ETV/TDF therapy in reducing the incidence of HCC in CHB patients with liver cirrhosis [7-10]. On the other hand, only small and usually statistically insignificant HCC-reducing effects of ETV/TDF were observed in patients without cirrhosis [7, 10]. Because the risk of HCC is much smaller in non-cirrhotic patients, it is conceivably difficult to perform meaningful comparisons between treated and untreated patients in studies with a small number of HCC events. Nevertheless, a recent propensity score-matched study with an 8-year follow-up by Nguyen and colleagues indicated that long-term TDF use as compared with no treatment was associated with a lower HCC risk in patients without cirrhosis [8].

The determinants of HCC occurring among treated patients are important to recognize but remain incompletely understood. In addition to cirrhosis, other demographic (e.g., age, and gender) and clinical variables (e.g., diabetes, serum platelet count, dynamic change of virological markers during antiviral therapy) have been variably reported to be associated with HCC risk among treated patients [11-18]. Predictive risk scores have incorporated some of these determinants; however, the performance and generalizability of these scores are unclear. Lastly, studies have reported conflicting results regarding differences in favor of TDF over ETV in HCC-reducing effects.

We, therefore, conducted a systematic review of the literature to answer the following questions:

(1) What is the magnitude of HCC risk in CHB patients receiving ETV/TDF therapy?

(2) Does the risk of HCC change over time in patients on long-term ETV/TDF treatment?

(3) What are predictive risk scores for HCC in patients receiving ETV/TDF?
(4) Do TDF and ETV differ in the effects of reducing HCC risk?

PATIENTS AND METHODS

The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline [19] (Supplementary Table 1:PRISMA check list). We searched the PubMed and EMBASE databases for all full articles published in English by using the following search terms and strategy: (hepatocellular carcinoma) AND (tenofovir OR entecavir OR telbivudine OR adefovir OR lamivudine) AND (hepatitis B) between January 1, 2006, and September 1, 2019 (Supplementary Table 2**)**. Because tenofovir alafenamide was not approved to treat CHB until late 2016, literature pertaining to its effectiveness for HCC prevention was not available. Manual searches for relevant articles were also performed, using the ancestry method [20]. We included studies if the enrolled patients with CHB were aged ≥ 16 years, if they were treated with either ETV or TDF, and if the studies reported HCC incidence > 1 year after ETV/TDF use. We excluded articles that enrolled patients treated with various antiviral agents for which separate data for patients on ETV and/or TDF monotherapy were not available, those that focused exclusively on outcomes after discontinuation of antiviral therapy, those that did not clearly report the HCC cumulative incidence, and those that consisted of fewer than 100 treated patients or patients exclusively co-infected with hepatitis C virus or human immunodeficiency virus. If the articles did not directly report HCC incidence but provided information of HCC events and person-time at risk, we calculated the HCC incidence according to such information. For studies that were based on the same cohort, we selected the most representative (largest or most recent). Two reviewers (CHT and CMT) independently selected and reviewed the screened articles; they resolved differences in opinion through discussion with a senior researcher (YCH).

RESULTS

The database search returned 1,436 results. Using Endnote,™ we found and removed 220 duplications as well as an additional 1,075 papers by screening titles and abstracts. In total, full text from 141 studies was reviewed; and 34 studies that fully met eligibility criteria were included in data synthesis **(Figure 1**).

HCC Incidence in CHB Patients on ETV/TDF Therapy according to Pretreatment Status of Liver Cirrhosis

For this topic, we included only articles that provided separate data for patients with and without cirrhosis (further categorized as compensated or decompensated). We identified 19 studies (10 from Asia) that fulfilled the inclusion and exclusion criteria, and the characteristics of enrolled studies were summarized in **Supplementary Table 3**. Only 1 study, for which the cohort was based on the TDF registration trial, defined the degree of liver fibrosis/cirrhosis by histopathology [21]; while the other 18 studies allowed clinical or imaging-based diagnosis for cirrhosis. HCC incidence rates varied widely across these studies [7, 8, 10, 18, 21-35]; in general, however, the 5-year cumulative incidence increased from patients without cirrhosis (0.5~6.9%) to patients with compensated (4.5~21.6%) and decompensated cirrhosis (36.3~46.5%) (**Figure 2)**. Among non-cirrhotic patients, the 5-year cumulative HCC incidence ranged from 0.5% to 3.7% in Caucasian and 1.9% to 6.9% in Asian population; and among compensated cirrhotic patients, the incidence were 9.52~17.5% in Caucasians and 18.4~21.6% in Asians, respectively. Intriguingly, HCC incidence among Caucasian patients was highest in the multinational European (PAGE-B) cohort than in the Spanish or Greek cohorts. Of note, the incidence was not reported in 4 enrolled articles but could be calculated according to HCC events and person-years at risk within the context [8, 21, 31, 34]. Information was provided at biennial intervals for 1 of the 4 studies (i.e., at 2, 4, 6, 8 years), and the 5-year HCC incidence was estimated by interpolation [8].

The Incidence Rate of HCC Change over Time in Patients Treated with ETV/TDF Therapy

We identified 4 studies that addressed changes in the incidence rate of HCC over time during treatment [13, 36-38] , and baseline characteristics were summarized in **Supplementary Table 4**. Papatheodoridis et al. reported in a multicenter European study that the annual HCC incidence was significantly lower after 5 years of treatment than within the first 5 years of

ETV/TDF treatment in Caucasian patients with cirrhosis. However, this effect was not observed in patients without cirrhosis [38]. Hsu et al. analyzed the national healthcare database from Taiwan and reported that the annual incidence of HCC significantly decreased every successive year during treatment [36]. The analysis was not further stratified by baseline cirrhosis. On the other hand, Kim et al. reported that the annual HCC incidence did not decrease significantly within and after the first 5 years of ETV treatment in a single-center cohort of Korean patients either with or without cirrhosis. However, the annual incidence of HCC was significantly lower after 7 years of treatment than within the first 7 years in patients with cirrhosis [13]. Kim et al. conducted a multicenter retrospective cohort study from Korea to develop an HCC risk score (mPAGE-B), indicating that the annual incidence of HCC decreased significantly after 4 years of ETV/TDF treatment compared to within the first 4 years treatment, both in low-risk (mPAGE-B score ≤ 8) , intermediate risk (mPAGE-B score 9-12), and high-risk (mPAGE-B score ≥ 13) patients [37]. The annual HCC incidence rates within 4 years vs within 4-8 years were 0.2% vs 0% in the low-risk, 1.1% vs 0.2% in the intermediate-risk, and 4.6% vs 1% in the high-risk groups, respectively. The results of included articles were summarized in **Table 1**,

Risk Scores for Predicting HCC Incidence during Long-term ETV/TDF Therapy

We identified 6 HCC risk-scoring systems that were developed using data of CHB patients on long-term ETV/TDF (**Table 2**) [16, 37, 39-42]. Only 1 scoring system (*p*latelets-*a*ge-*g*end*e*r in Caucasians with chronic hepatitis *B* [PAGE-B]) was derived using data from a Caucasian study population [40], whereas the other 5 (HCC-*r*isk *e*stimating *s*core in *C*HB patients *u*nder *E*ntecavir [HCC-RESCUE], *a*ge-*p*latelet-*a*lpha fetoprotein in Asian patients with chronic hepatitis *B* [APA-B], the modified PAGE-B [mPAGE-B], *c*irrhosis-*a*ge-*m*ale sex-*d*iabetes mellitus [CAMD], and *a*ge-*a*lbumin-*s*ex-*l*iver cirrhosis-HCC [AASL-HCC]) have used data from Asian populations [16, 37, 39, 41, 42]. The mPAGE-B score was developed in South Korea by modifying the PAGE-B score with the addition of serum albumin levels [37].

All these scores included age, sex and markers of liver fibrosis and hepatic function, such as platelet counts and albumin levels. The CAMD risk score also included diabetes mellitus status in the formulation [39]. The APA-B score included on-treatment alpha fetoprotein levels and platelet counts after 12 months of ETV treatment [16]. Among the 6 scoring systems, the CAMD, mPAGE-B, and PAGE-B scores have been externally validated in subsequent independent studies [16, 35, 37, 39, 42-46]. The results of studies that performed comparisons among

these 6 scoring systems are summarized in **Table 3**. Generally, the validation results of each scoring system showed acceptable discrimination, with the concordance rates between 0.76~0.86 for HCC at 5 years in the validation cohorts. None of the scores developed from Asian populations have been externally validated in Europe or North America. The PAGE-B scoring system, which was derived using data from a Caucasian study population, is the only score validated in both the West and East. Of note, only 2 independent studies validated and compared the risk scores using patient data explicitly external to the populations for which the scores were developed. Kim et al. reported that the CAMD score was superior to PAGE-B but not different from mPAGE-B, while the latter 2 scores were similar in performance [46]. Lee and colleagues also found similar performance between the mPAGE-B and PAGE-B scores [45].

TDF and ETV Differences in Preventing HCC Occurrence

The study by Choi and colleagues was the first to report a difference between TDF and ETV in HCC-preventing effects [47]. In this Korean study, patients treated with TDF had significantly lower HCC incidence in a national insurance claims database cohort (hazard ratio [HR]: 0.68; 95% confidence interval [CI]: 0.60–0.85), as well as the hospital-based validation cohort (HR: 0.68; 95% CI: 0.46–0.99). For this issue, 7 comparative studies of TDF and ETV were identified and summarized in **Table 4** [11, 30, 47-51]. All these studies were conducted in Asian populations and based on observations from retrospective cohorts. Only 4 studies employed matching techniques to enhance comparability between the 2 treatment groups [30, 47, 49, 51]. Among them, only the study by Choi and colleagues observed statistically significant differences between patients treated with TDF and ETV.

Two meta-analyses examining the comparative effectiveness of TDF versus ETV in preventing HCC arrived at different conclusions [52, 53]. Zhang et al. indicated that TDF was more effective than ETV after reviewing 7 studies [53], whereas Wang et al. found no significant differences between the 2 regimens from pooled analysis of 8 studies [52]. Of note, only 3 studies were common to both meta-analyses. Among the individual articles included were studies that reported comparative HCC data only in number or proportion, rather than incidence of the event [35, 54-56]. Importantly, neither meta-analysis included the multicenter study by Kim et al. [30] from South Korea, which confined the enrollment period to after 2012, when both ETV and TDF became similarly available as first-line therapy in their country.

DISCUSSION

This systematic review addressed several aspects of the impact of long-term ETV/TDF therapy on risk of HCC in patients with CHB. First, the residual risk of HCC remarkably differs, according to the liver fibrosis stages /cirrhosis at treatment initiation. Second, the HCC incidence rate decreases over time on long-term ETV/TDF therapy, particularly among patients with liver cirrhosis. Third, there are 6 validated risk scores for HCC prediction in patients with long-term viral suppression. However, most were developed from Asian patients; and their generalizability to Western populations is not known. Fourth, available evidence is conflicting and inconclusive as to differential HCC reducing effect between TDF and ETV.

Not surprisingly, HCC incidence rates increased from non-cirrhotic to compensated cirrhotic, then to decompensated cirrhotic patients; however, the incidence rates varied widely across studies, which may have been due to heterogeneous patient characteristics (age, sex, genotype, race and previous treatment), different indications of ETV/TDF, different tools to measure fibrosis or define cirrhosis, or differences in the screening method or interval. Regardless, these results strongly suggest the benefits of initiating HBV treatment early to prevent patients from progressing to liver cirrhosis or advanced fibrosis.

In natural history studies, the incidence of HBV-related HCC reportedly differed between Asians and Caucasians, possibly due to differences in the mode and timing of HBV transmission or distribution of viral genotypes [57, 58]. In contrast, HCC incidence while on antiviral therapy in the Caucasian population appears to be comparable with that in the Asian population or populations with mixed ethnicities (**Figure 2**). Interestingly, HCC incidence was particularly high in the PAGE-B cohort among non-cirrhotic Caucasian populations [26]; but it seems just slightly lower than the highest results from the Asian counterparts [23, 29, 30]. Regardless, no comparative multi-ethnicity studies address the Asian vs Caucasian risk of HCC in patients treated with TDF or ETV.

We found that the annual HCC incidence rates decreased numerically over time among patients on ETV/TDF treatment in most studies. The insignificant results in some studies may have been due to inadequate statistical power, particularly in patients without cirrhosis. With regards to explanations for the declining HCC risk over time, older age and competing causes of mortality could have played a role despite the adjustments for this factor in some studies[36].

The bulk of existent literature in therapeutic efficacy of ETV/TDF, however, suggested that treatment effect was causally related (at least in part) to the gradual decline in HCC incidence rates. For instance, long-term ETV/TDF therapy can result in regression of liver fibrosis,[59, 60] which is the major HCC risk determinant. Furthermore, sustained viral inhibition precludes the release of infectious virions, thus reduces the amount of infected hepatocytes in the long run, and thereby blocks the upstream process of HBV-induced hepatocellular carcinogenesis. Therefore, it appears reasonable to expect the longer patients stay on ETV/TDF treatment, the lower their residual HCC risk will remain. But the treatment duration required to lower the HCC incidence to a negligible level is unclear; and hepatocellular carcinogenesis may still accrue from preexistent integration of HBV DNA into the host genome, despite profound inactivation of viral transcription and translation [61].

In the natural history of CHB, replicative and translational activities of the virus are the major driving forces for liver disease progression. Several biomarkers, including serum viral load, hepatitis B e antigen status, and serum levels of hepatitis B surface antigen, were found to be predictive of HCC development [2, 62, 63]. However, the association of virological biomarkers with incident HCC was not significant in patients continuously treated with antiviral therapy [16, 37, 40-42]. Current evidence indicates that host factors, such as age, sex, status of fibrosis or cirrhosis, severity of hepatic dysfunction, and diabetes mellitus, are major HCC risk factors in treated patients [16, 17, 37, 39-41]. The dynamic changes in levels of serum markers, such as elevation of alpha-fetal protein[18] , low platelet count [16], detectable viremia [13], and elevated alanine aminotransferase levels [12] are additional on-therapy risk factors for HCC. Novel biomarkers such as Mac-2 binding protein glycan isomer [14, 15] or hepatitis B core-related antigen [64, 65] have been tested, with early promising results, and further investigation is warranted to facilitate personalized risk stratification.

The component factors appear similar among the 6 HCC predictive risk scores, but the exact variables and their weighting are different. For example, the presence of cirrhosis was not included in PAGE-B or mPAGE-B; whereas it was heavily weighted in the CAMD, AASL-HCC, and HCC-Rescue scores. In fact, cirrhosis was a significant risk factor for HCC in the multivariable regression model in the development of the PAGE-B score but it was not included in the formula because the authors found its inclusion did not considerably improve discrimination (*c* indices of the formulas with and without cirrhosis were 0.84 and 0.82, respectively, in the development study). The CAMD scoring system is uniquely free of

laboratory tests, and it also takes into account the interaction between age and cirrhosis in estimating HCC risk [39]

How these risk scores may improve clinical practice is not yet clear. In theory, accurate risk stratification can direct high-risk patients to more intensive HCC surveillance or additional interventions if available to reduce the risk further. On the other hand, the low-risk patients can forgo HCC surveillance. Empirical data from daily practice is essential to confirm such clinical utility. All these 6 risk scores use clinically convenient variables and appear readily applicable to most CHB patients about to start therapy. According to our review of current literature, CAMD, PAGE-B, and mPAGE-B have undergone external validation by independent studies with satisfactory results and may be preferred over other scores for clinical application. Of note, PAGE-B was developed early and is also the only risk score that has been validated in both Western and Eastern populations. Moreover, outcome research is warranted to appraise the effectiveness of application of a risk score in clinical practice. Ideally, such research should adopt an interventional or quasi-experimental design.

There are limitations in currently available risk scores and some questions remain unanswered. First, current scores use baseline parameters when patients started the treatment or items 12 months after therapy. Therefore, the risk of HCC is determined at treatment initiation and fixed thereafter. Such approach cannot reflect the dynamic changes in risk determinants and thus may not accurately predict the time-varying HCC risk along the treatment course. For example, it is unclear how to evaluate the risk of HCC following regression of liver cirrhosis in patients who start antiviral treatment with cirrhosis. In addition, most scores cannot be applied to already treated patients with missing baseline data required for score calculation. Furthermore, these scores may not comprehensively include risk factors that affect HCC development. For instance, none of the risk scores was able to cover genetic predisposition or environmental exposure (e.g., alcohol, aflatoxin, or air pollution) in the development study. Finally, performance of the risk scores developed in Asian patients remain unknown in the Caucasian populations and requires validation. Recently, a newly developed scoring system, the *R*eal-world *E*ffectiveness from the *A*sia Pacific Rim *L*iver Consortium for H*B*V (REAL-B) score [66], was the first to be developed from CHB patients receiving antiviral treatment both in the East (Asia-pacific countries) and the United States. Nevertheless, it was not dedicated to patients treated with TDF or ETV and, thus, was not covered in this review.

Only 1 of the 7 studies identified in our review reported significantly lower risk of HCC among TDF users than ETV users. The comparative effectiveness of TDF versus ETV in HCC prevention is an ongoing debate, and the expectation is that more studies will occur. The biological mechanisms to explain the superiority of TDF over ETV involved the carcinogenic potential of ETV and more potent induction of interferon-λ3 by TDF than by ETV [47]. However, the ETV carcinogenic effect was observed in mice treated with ETV doses much higher (>100 fold) than those used in humans; and excessive cancer risks were not observed in long-term ETV studies [67, 68] . In the study by Choi et al., the virological response defined by serum HBV viral load less than 60 IU/mL at 1 year was significantly lower in the ETV group than in the TDF group (77.1% vs. 84.8%, $P < 0.001$), and switching or adding another antiviral agent was significantly higher in the ETV than in the TDF group (11.7% vs. 0.2%, $P < 0.001$). On the other hand, Kim et al. found similar risks of HCC between TDF and ETV receivers who started the therapy after the same time point (i.e., 2012) and suggested that the later availability of TDF and its delayed uptake in clinical practice could confound the association of antiviral regimens with the risk of HCC. Given the importance of this issue, more data are required to untangle the controversy.

Our review has both strengths and weaknesses. The strengths of our review are the systematic approach to search relevant literature, prespecified criteria to select studies, and separation of HCC incidence among patients with/without cirrhosis to provide more detailed information for clinical practice. The TDF vs ETV comparison was addressed with updated data from the study by Kim et al.[30], although so far the controversy remains unsettled. There are some limitations in our systematic review. First, our review are related to the individual studies being observational and mostly retrospective and, thus, susceptible to misclassification of exposures and outcomes, as well as missing data. Second, meta-analysis is beyond the scope of our study, further research is needed to provide solid data for each specific question.

CONCLUSIONS

The residual risk of HCC in CHB patients on ETV/TDF therapy remains substantial, particularly for patients already presenting with liver cirrhosis at treatment initiation. Nevertheless, the risk will decline over time during long-term treatment. There have been 6 risk scores (AASL-HCC, APA-B, CAMD, HCC-RESCUE, mPAGE-B, and PAGE-B) dedicated to predict occurrence of incident HCC in patients on ETV/TDF treatment, with

external validation of some (CAMD, mPAGE-B, and PAGE-B). However, clinical application and generalizability of these models warrants further research. The evidence is not consistent among the comparative ETV versus TDF studies on HCC- reducing effectiveness and, therefore, no conclusion is possible without additional research.

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Table 1: Summary of included studies reporting changes in HCC incidence over time on TDF or ETV therapy

	Cohort	HCC annual incidence over time				Remarks
Kim [37] 2018 Asian (Korea)	n=3,001 Cirrhosis: 19.5% Follow-up (months): 49 [a] Medication: TDF or ETV		Year 0–4	Year 4–8	*P* value	Annual incidence of HCC significantly decreased over time in all populations and every risk group.
		Low risk	0.2%	0%	0.03	
		Intermediate risk	1.1%	0.2%	<0.001	
		High risk	4.6%	1%	<0.001	
Kim [13] 2018 Asian (Korea)	n=894 Cirrhosis: 49.2% Follow-up (months): 60 [b] Medication: ETV		Year 0-5	Year 5-10	*P* value	The incidence of HCC significantly decreased after 7 years of treatment than within the first 7 years in patients with cirrhosis.
		All	2.29%	1.66%	0.217	
		Non-cirrhosis	0.31%	0.43%	0.739	
		Cirrhosis	4.16%	2.83%	0.155	
		PS: The incidence of HCC (<7 Y vs >7 Y) significant decrease in cirrhotic patients: 4% vs. 1.42% (*P* = 0.02)				
Hsu [36] 2018 Asian (Taiwan)	n=27,820[c] Cirrhosis: 33.2% Follow-up (months): 25.1 [b] Medication: TDF or ETV	1 Y	2 Y	3 Y	*P*	The incidence of HCC significantly decreased every successive year in the study population overall without further categorization by cirrhosis status.
		1.87%	1.28%	1.07%	< 0.001	
Papatheodoridis [38] 2017 Caucasian	n=1,951 Cirrhosis: 27% Follow-up (months): 72 [b] Medication: TDF or ETV		Year 0–5	Year 5–10	*P* value	HCC risk decreased significantly beyond 5 years of TDF or ETV in Caucasian population with cirrhosis
		All	1.22%	0.73%	0.05	
		Non-cirrhosis	0.49%	0.47%	0.93	
		Cirrhosis	3.22%	1.57%	0.039	

a: Median; b: Mean; c: The only one study enrolling HCV coinfection patients among the studies in this review.

Abbreviations: HCC, hepatocellular carcinoma; ETV, entecavir; IRRs: incidence rate ratios; TDF, tenofovir disoproxil fumarate; TE, treatment experienced.

Table 2: Summary of risk scores developed from CHB patients on TDF or ETV therapy to predict incident HCC

	AASL-HCC	CAMD	mPAGE-B	APA-B	HCC-RESCUE	PAGE-B
	Yu[42]	Hsu[39]	Kim[37]	Chen[16]	Sohn[41]	Papatheodoridis[40]
	2019	2018	2018	2017	2017	2016
Race (Country)	Asian (Korea)	Asian (Taiwan)	Asian (Korea)	Asian (Taiwan)	Asian (Korea)	Caucasian (Greece, Italy, Spain, Netherlands, Turkey)
Number	944	23,851	2,001	883	990	1,325
Age	50 [b]	47.5 [b]	Age: 50 [b]	50 [c]	47.4[c]	52[c]
Cirrhosis (%)	39.3%[a]	26.5%	19.1%	35.9%	39%	20%
Prior nucleos(t)ide (%)	All naïve	All naive	39.5%	All naïve	All naïve	33%
Antivirals	ETV/TDF	ETV/TDF	ETV/TDF	ETV	ETV	ETV/TDF
Follow-up (month)	48.6 [b]	25.8 [b]	49 [b,d]	49.1 [b,d]	25.2 [b]	44 [c]
HCC incidence	6.5%(5Y).13.9%(10Y)	3.56%(3Y)	6.6%(5Y)	2.2%(2Y). 3.4%(3Y). 10.3%(5Y). 13.7%(7Y)	1.5%(1Y). 5%(3Y). 11.2%(5Y)	5.7%(5Y)
Risk parameter	Age Sex Cirrhosis Albumin	Age Sex Cirrhosis Diabetes	Age Sex Platelet Albumin	Age (12 months after ETV) Platelet (12 months after ETV) AFP (12 months after ETV)	Age Sex Cirrhosis	Age Sex Platelet
Risk stratification according to the scores	Low risk ≤ 5, 5-year incidence: 0% High risk ≥ 20, 5-year incidence: 17.6%	Low risk < 8, 3-year incidence: 0.27% High risk >13, 3-year incidence: 10.75%	Low risk ≤ 8, 5-year incidence: 1.9% High risk ≥ 13 5-year incidence: 18.2%	Low risk ≤ 5, 5-year incidence: 3.33% High risk ≥ 10,5-year incidence: 49.50%	Low risk ≤ 64, 5-year incidence: 0.5% High risk ≥85, 5-year incidence: 37.1%	Low risk < 10, 5-year incidence: 0% High risk >17, 5-year incidence: 17%
External validation in independent studies	No	Yes	Yes	No	No	Yes

a: Including patients with decompensated cirrhosis; b: Median; c: Mean; d: Follow-up period of the total cohort (development and validation cohort).

AFP, alpha-fetal protein; CHB, chronic hepatitis B; ETV, entecavir; HCC, hepatocellular carcinoma; TDF, tenofovir disoproxil fumarate

Table 3: Summary of studies on comparison of risk scores dedicated to HCC prediction during TDF or ETV therapy

	Comparison	Validation cohort	Results of concordance index	Remarks
Independent studies externally validate different risk scores				
Kim SU[46] 2019	CAMD vs. mPAGE-B vs. PAGE-B	Number: 3277 (Korea) Age: 48.7 (mean)	CAMD vs. mPAGE-B vs. PAGE-B 0.79 vs. 0.769 vs. 0.76 (5-year incidence)	CAMD is significantly superior to PAGE-B and not different from mPAGE-B
Lee[45] 2019	mPAGE-B vs. PAGE-B	Number: 1330 (Korea) Age: 48.1 (mean)	mPAGE-B vs. PAGE-B 0.785 vs. 0.751[a] (entire study period, unspecified)	mPAGE-B is similar with PAGE-B
Comparative studies from the original risk score developing studies				
Yu[42] 2019	AASL-HCC vs. PAGE-B[c]	Number: 944 (Korea) Age: 50 (median)	AASL-HCC vs. PAGE-B 0.814 vs. 0.719 (5-year incidence)	AASL-HCC is significantly superior to PAGE-B
Hsu[39] 2018	CAMD vs. PAGE-B	Number:17,984 (Hong Kong)[b] Age: 52.1 (median)	CAMD vs. PAGE-B 0.74 vs. 0.73 (3-year incidence) 0.75 vs. 0.74 (5-year incidence)	CAMD is not different from PAGE-B[b]
Kim JH[37] 2018	mPAGE-B vs. PAGE-B	Number:1000 (Korea) Age: 50 (median)	mPAGE-B vs. PAGE-B 0.82 vs. 0.72 (5-year incidence)	mPAGE-B is significantly superior to PAGE-B
Chen[16] 2017	APA-B vs. PAGE-B[c]	Number: 883 (Taiwan) Age: 50 (mean)	APA-B vs. PAGE-B 0842 vs. 0.742 (3-year incidence) 0.827 vs. 0.696 (5-year incidence)	APA-B is significantly superior to PAGE-B[c]

Only the studies from Kim SU [46] and Lee [45] were independent studies in patients unrelated to the populations where risk scores were developed. The other validation studies came from the risk score development studies [16, 37, 39, 42].

a: this cohort included patients receiving lamivudine, and the comparison is the result of subgroup analysis for patients receiving ETV/TDF; b: the Hong Kong cohort comprised 19,321 patients in total but data of platelet count were available in only 17,984 patients for the comparison of CAMD versus PAGE-B scores; c: comparison with the PAGE-B score was performed in the development cohort of the APA-B score.

ETV, entecavir; HCC, hepatocellular carcinoma; TDF: tenofovir disoproxil fumarate.

Table 4: Summary of studies directly comparing HCC incidences between patients treated with TDF versus ETV

	Matched cohorts	Medication	Number	Cirrhosis (%)	Age	Male (%)	Follow-up (months)	VR[a] (%)	HCC incidence
Kim SU [30]	Yes	TDF	1278	31.3	48.2[c]	62.1	Unspecified[g]	87.5 (2-year)	5-year HCC incidence
Asian (Korea)		ETV	1278	30.8	48.6[c]	62.1	Unspecified[g]	86.5 (2-year)	TDF vs. ETV: 7.9% vs 8.7%; *P* = 0.884 ; HR: 1.021 (95% CI, 0.773-1.349)
Kim BG[49]	Yes	TDF	354	44.1	51[c]	62.7	32.9[c]	94.5 (5-year)[f]	Annual incidence:
Asian (Korea)		ETV	354	47.7	51[c]	62.1	48.1[c]	98.2 (5-year)[f]	TDF vs. ETV: 072% vs. 1.69%; *P* = 0.142; HR: 053 (95% CI, 0.8-4.5)
Choi[e 47]	Yes	TDF	869	58.1	48.8[c]	62.1	32[d]	84.8 (1-year)	Annual incidence:
Asian (Korea) Hospital cohort		ETV	869	58.8	48.8[c]	59.7	48[d]	77.1 (1-year)	TDF vs. ETV:1.37% vs. 2.17%; *P* = 0.04; HR: 0.68 (95% CI, 0.46-0.99)
Kim YM[50]	No	TDF	112	26.8	49.3[c]	62.5	38.5[c]	91.9[b]	Annual incidence:
Asian (Korea)		ETV	191	27.8	47.4[c]	60.7	66.6[c]	94.2[b]	TDF vs. ETV: 085% vs. 1.27%; *P* = 0.526
Yu JH [11]	No	TDF	176	43.8	49[d]	59.1	33.6[d]	83.4 (1-year)	4-year HCC incidence
Asian (Korea)		ETV	406	36.5	53[d]	67	69.9[d]	81.5 (1-year)	TDF vs. ETV: 5% vs. 4%; *P* = 0.471
Wu [51]	Yes	TDF	106	27.4	47.1[c]	70	37.9[c]	87.7 (3-year)	4-year HCC incidence
Asian (Taiwan)		ETV	212	26.9[a]	46.3[c]	76.4	47.8[c]	90.9 (3-year)	TDF vs. ETV: 7.7% vs. 5.1% ; *P* = 0.38
Köklü [48]	No	TDF	72	100	54.2[c]	75	21.4[c]	92.2 (1-year)	HCC occurred in 2 and 4 TDF and ETV receivers,
Asian (Turkey)		ETV	77	100	52.4[c]	77.9	24[c]	96.6 (1-year)	respectively, without between-group differences (*P*=0.43) in HCC-free time, but the incidences were not reported.

a: the definition of VR varied among studies; b: during follow up. c: mean. d: median. e: for the hospital-based cohort; f: before matching; g: a median follow-up of 59.2 months for the entire study population.

CI, confidence interval; ETV, entecavir; HCC, hepatocellular carcinoma; HR, hazard ratio; TDF, tenofovir disoproxil fumarate; VR, virological response.

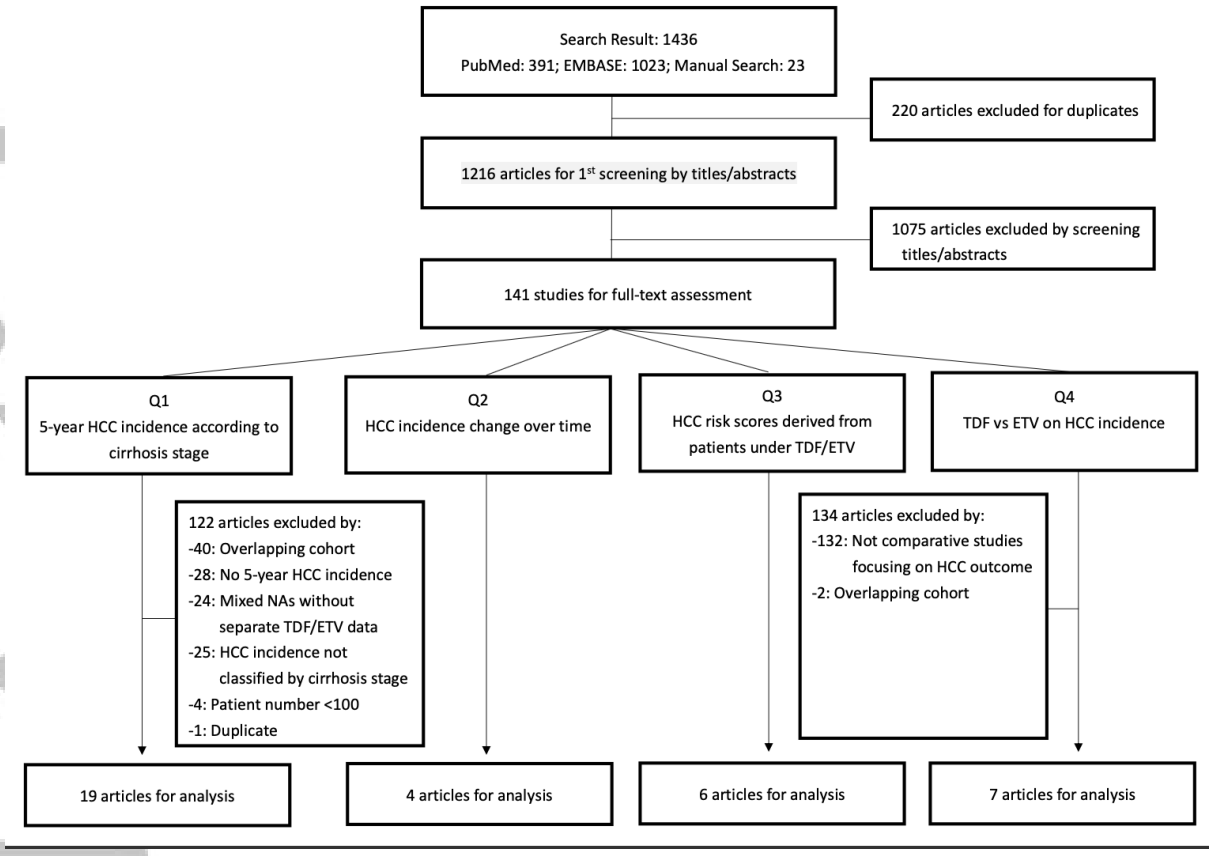

Figure 1. Flow diagram for the selection of studies

Abbreviation: ETV, entecavir; HCC, hepatocellular carcinoma; HR, hazard ratio; NAs, nucleos(t)ide analogues, TDF, tenofovir disoproxil fumarate.

Figure 2. Five-year cumulative probability of hepatocellular carcinoma under long-term tenofovir or entecavir treatment in patients with chronic hepatitis B according to cirrhosis status. 1A (upper panel): without cirrhosis (Reference [7, 8, 10, 21-27, 30-33, 35]); 1B (middle panel): with compensated cirrhosis (Reference [18, 21, 26, 28-30, 34]); 1C (lower panel): with decompensated cirrhosis (Reference [26, 29]).

(a): The 5-year cumulative incidence, which was not shown in the original article, was estimated according to HCC events and patients at risk with the context.

(b): 2.9% in ETV group, and 3.8% in TDF group (The overall incidence of ETV and TDF was not available, the graphic bar showed the higher one)

(c): 4.6% in patients with maintained viral response, and 6.9% in low-level viremia.

(d):16.8% in TDF group, and 21.6% in ETV group