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REVIEW

Comparison of tenofovir versus entecavir for preventing hepatocellular carcinoma in chronic hepatitis B patients: an umbrella review and meta-analysis

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Abstract

There are several meta-analyses about the comparison of tenofovir disoproxil fumarate (TDF) versus entecavir (ETV) for preventing hepatocellular carcinoma in patients with chronic HBV infection published in recent years. However, the conclusions vary considerably. This umbrella review aims to consolidate evidence from various systematic reviews to evaluate differences in hepatocellular carcinoma prevention between two drugs. Systematic searches were conducted using PubMed, Embase, and Web of Science to identify original meta-analyses. Finally, twelve studies were included for quantitative analyses. We found that TDF treatment was associated with a significantly lower risk of HCC than ETV (hazard ratio, 0.80; 95% CI 0.75–0.86, $p < 0.05$). The lower risk of HCC in patients given TDF compared with ETV persisted in subgroup analyses performed with propensity score-matched cohorts, cirrhosis cohorts, nucleos(t)ide naïve cohorts and Asian cohorts. In the cohorts of non-Asia and patients without cirrhosis, there was no difference exhibited between these two drugs. Subsequent analyses showed TDF treatment was also associated with a lower incidence of death or transplantation than patients receiving ETV. Overall, the preventive effect of these two drugs on HCC has been studied in several published meta-analyses, but few were graded as high-quality evidence, meanwhile, most of which had high overlap. Thus, future researchers should include updated cohorts or conduct prospective RCTs to further explore this issue.

Keywords Nucleos(t)ide analogue · Chronic hepatitis B · Hepatocellular carcinoma · Umbrella review · Meta-analysis

Introduction

Current WHO data indicate 254 million persons living with CHB resulting in 1.1 million deaths annually (EASL 2017; Omata et al. 2017; Marrero et al. 2018; El-Serag 2012). For patients with chronic hepatitis B (CHB), hepatocellular carcinoma (HCC) is the main cause of death. The sustained replication of HBV is the main driving factor of the progression from CHB to cirrhosis and even HCC (Chen et al. 2006). Suppressing HBV replication using long-term nucleos(t)ide analogue (NA) therapy can reduce the risk of HCC and mortality in CHB patients (Hosaka et al. 2013; Wong et al. 2013). According to current international practice guidelines, the two NA TDF and ETV are recommended as first-line antiviral agents for CHB, because of their high antiviral efficacy and low rate of resistance (Terrault et al. 2018). However, it has not yet been determined whether there is a difference in the effectiveness of these two drugs in preventing HCC.

Randomized-controlled trials (RCTs) are the gold standard of evidence for comparing treatment efficacy, yet few addressed this topic. Two RCTs compared TDF and ETV recently, however, the observed incidence of HCC was too low to allow for meaningful comparisons of HCC risk (Sriprayoon et al. 2017; Cai et al. 2019). Several meta-analyses have synthesized data from observational studies, but results comparing the two drugs remained conflicting,

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thus hampering our ability to draw specific conclusions and reveal implications for clinical practice. Some researchers believed that patients receiving TDF had a lower risk of HCC (Choi et al. 2021; Cheung et al. 2020; Gu et al. 2020; Shao et al. 2023; Yuan et al. 2022), while others argued that there was no difference in the efficacy of the two drugs (Tseng et al. 2020; Dave et al. 2021; Yuan et al. 2021; Li et al. 2020). However, although the authors of the existing meta-analysis have tried their best, the number of included primary studies was still limited, and the subgroups divided were not comprehensive enough. Furthermore, the methodological quality of the meta-analyses and the quality of evidence remain to be assessed by validated tools.

In the research field where many meta-analyses have been conducted, a promising way to integrate the existing evidence is to conduct an umbrella review, which systematically synthesizes the findings from multiple systematic reviews, in order to provide a comprehensive and up-to-date summary of relevant research (Türk et al. 2023). The conclusion of an umbrella review may not be of novelty that completely differs from current systematic reviews, but its purpose is to provide an overall assessment of existing systematic reviews for a specific question (Aromataris et al. 2015), thereby identifying areas of consensus, highlighting discrepancies, and pointing out deficiencies.

Our umbrella review aims to critically evaluate and summarize the evidence from systematic reviews up to now regarding the HCC risk in different subgroups of CHB patients receiving TDF versus ETV treatment, through which provide a comprehensive overview of the current evidence, aid clinical decision-making, and guide the design and implementation of future clinical trials.

Methods

Our protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) and assigned registration number CRD42023494010. To take the highest quality approach we followed the Cochrane Handbook guidelines (Pollock et al. 2023) for conducting "Overview of reviews" and the preferred reporting items for systematic reviews and meta-analysis (PRISMA) Statement (Moher et al. 2009) in reporting our umbrella review.

Search strategy

Two authors conducted a systematic literature search in PubMed, EMBASE, Web of Science, and Cochrane Library databases until September 2023 to identify published meta-analyses investigating the HCC risk in CHB patients receiving TDF versus ETV. In addition, we hand-searched reference lists of identified meta-analyses and relevant review articles. Any disagreements were resolved by discussion and consensus.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) meta-analyses based on at least two primary studies, which includes RCT, nonrandomized prospective or historical cohort studies; (2) patients with CHB; (3) accepting TDF or ETV monotherapy; (4) meta-analyses that have reported the hazard ratio (HR) with 95% confidence interval (CI) for the risk of HCC in patients receiving TDF versus ETV;

The exclusion criteria were as follows: (1) no summary estimate was reported (e.g. systematic reviews without meta-analysis); (2) meta-analyses that included patients co-infected with hepatitis C virus or human immunodeficiency virus; (3) using relative risk (RR), odds ratios (OR) or HCC incidence rate to synthesize the results of primary studies (4) comparing multiple antiviral drugs not only TDF or ETV.

Data extraction

Data were extracted by one author and double-checked by another author. For each published meta-analysis, we extracted the following data: name of the first author, publication year, number of included studies, study design of the primary studies, total number of cases and participants, quality assessment methods, subgroup classification of the entire CHB patients, unadjusted and adjusted HR with 95% CI synthesized using results of primary studies.

For each primary study, we extracted the first author's name, year of publication, number of total cases, number of participants, and unadjusted HR or HR that adjusted for the most confounders, along with their 95% CI.

Assessment of methodological quality

Since there is no standard for assessing the quality of meta-analysis yet (Türk et al. 2023), and the Cochrane guidelines (Pollock et al. 2023) points out "cannot currently recommend one tool over another due to a lack of empirical evidence on this topic", we adopted the validated AMSTAR 2 tool (a measurement tool to assess systematic reviews) (Shea et al. 2007, 2009, 2017, 2007) to evaluate the methodological quality of each included meta-analysis. It includes 16 items about the conduct of a meta-analysis, including the literature search, study selection and data extraction, reporting of included and excluded studies, quality assessment of the included studies, statistical methods for the meta-analysis, publication bias, and conflict of interest. Seven of these (item 2, 4, 7, 9, 11, 13 and 15) are considered critical as they can significantly

impact the validity of a review and its conclusions. Each question can be answered with "yes", "no" and "Partial Yes". This procedure has been applied successfully in previous umbrella review (Neuenschwander et al. 2019; Jaff et al. 2023).

AMSTAR 2 is not designed to generate an overall "score". A high score may disguise critical weaknesses in specific domains. In making an overall rating of systematic review it is important to take account of flaws in critical domains, which may greatly weaken the confidence that can be placed in a systematic review. The methodological quality of included meta-analysis was rated as high (no or one non-critical weakness), moderate (more than one non-critical weakness), low (one critical flaw with or without non-critical weaknesses) and critically low (more than one critical flaw with or without non-critical weaknesses) according to the quantity of critical and non-critical weaknesses (Shea et al. 2017).

Assessment and stratification of evidence quality

We evaluated the certainty for each outcome presented in the umbrella review through the grading of recommendations assessment development and evaluation (GRADE) approach (Guyatt et al. 2008) and classified evidence into "high," "moderate," "low," and "very low" quality. In this approach, direct evidence from RCTs starts at high confidence and can be rated down based on the risk of bias, indirectness, imprecision, inconsistency (or heterogeneity), and/or publication bias to levels of moderate, low, and very low confidence. Direct evidence from observational studies starts at low confidence and can be rated down for the previously mentioned factors or rated up if the magnitude of effect is large, or a dose–response effect is observed; where evidence was derived from both RCTs and observational studies, we conservatively attributed certainty to the lower level of evidence.

We also identified evidence that had the strongest evidence and no signals of large heterogeneity or bias according to the guideline by Fusar-Poli et al. (Fusar-Poli and Radua 2018). Specifically, we considered as convincing (class I) the evidence that fulfilled all the following criteria: when number of cases > 1000, statistical significance at $p < 10^{-6}$, low between-study heterogeneity $I^2 < 50\%$, 95% prediction interval excluding the null, no small-study effects and no excess significance bias. Evidence with > 1000 cases, $p < 10^{-6}$, and class I criteria not met were graded as highly suggestive (class II). Evidence with > 1000 cases, $p < 10^{-3}$, and class I-II criteria not met were considered suggestive (class III). The remaining nominally statistically significant evidence was considered weak (class IV). Evidence with $p > 0.05$ was considered non-significant.

Primary study overlap

A non-ignorable special issue is the possibility of overlapping primary studies in individual meta-analyses. To ensure statistical independence of effect sizes, it is usually recommended that each primary study only appear once in the final analyses (Türk et al. 2023). We created a citation matrix for main subgroups in the included systematic reviews separately to visualize the degree of overlap, and we calculated the corrected covered area (CCA). The CCA is a measure representing the overlap (relative coverage) of primary studies in the included meta-analyses: a CCA between 0 and 5 demonstrates slight overlap, 6 to 10 demonstrates moderate overlap, a score between 11 and 15 is considered high overlap, and > 15 very high overlap (Pieper et al. 2014).

Data analysis

HR with 95% CI adjusted by multivariable analysis or, preferentially, if possible, propensity score matching (PSM) was exacted from the primary studies. All the data synthesis was performed using DerSimonian and Laird random-effects models by weighting each effect size by its inverse variance, which takes into account heterogeneity both within and between studies. Between-study heterogeneity was calculated using Higgins' I^2 statistics. $I^2 < 50\%$ was considered low heterogeneity, and the fixed effect model was used for analysis instead. Individual effects and pooled mean effect sizes were summarized in forest plots for each outcome. Publication bias was visualized using funnel plots, and funnel plot asymmetry was assessed using Egger's and Begg's test. All tests were 2-sided, and P-value less than 0.05 was considered statistically significant.

Results

Study selection

Our preliminary literature search yielded 1298 relevant studies. After the screening process, 12 meta-analyses ultimately met our inclusion criteria and were included in qualitative synthesis (Fig. 1).

Description of included meta-analyses

An overview of the main characteristics of included meta-analyses was presented in (Table 1). Eligible meta-analyses were published between 2020 and 2023 including primary studies conducted between 2013 and 2021. All primary studies were retrospective. On average, meta-analyses included 17.5 primary studies with a range from 7 to 32

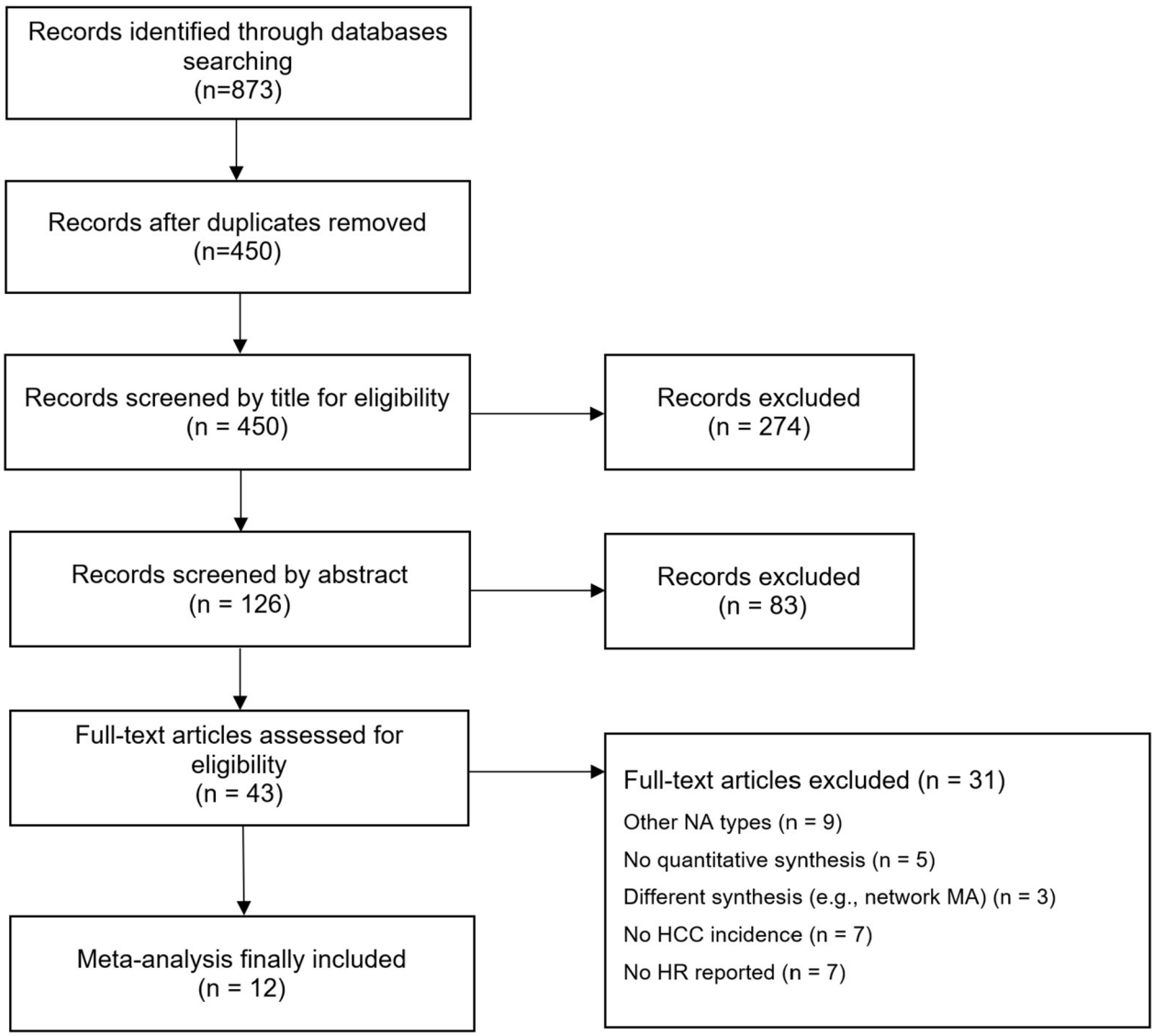

Fig. 1 Flow chart of literature search and screening process

studies. Sample sizes ranged between 24269 and 263947 participants in the included meta-analyses with an average of 89772 subjects per meta-analysis. Each meta-analysis reported the results of 9 subgroups on average by the form of HR with 95% CI with the number of subgroups ranging from 1 to 23. Among these subgroups reported in the included meta-analysis, results of the entire cohort without covariate adjustment were reported 5 times, results of the entire cohort adjusted by the multivariable analysis were reported 7 times, results from PSM cohorts were reported 9 times, results from NA treatment-naïve subgroups were reported 8 times and results from cirrhotic patients were reported 9 times, and 6 meta-analyses reported results in Asian and non-Asian CHB patients. In addition, 4 meta-analyses reported results at different follow-up times.

Among the 12 meta-analyses included, 2 were considered as convincing evidence, 4 as suggestive evidence, 3 as weak evidence and 3 as non-significant.

Methodological quality of included meta-analyses

The quality scores of each meta-analysis were based on the AMSTAR 2 tool. Overall scores with the single items were shown in (Supplementary Table S1). The included meta-analyses were rated as high for 16.7% (n = 2) studies, moderate for 25% (n = 3), low for 25% (n = 3), and critically low for 33.3% (n = 4). In general, the main flaws of meta-analyses rated as low or critically low in quality were that the authors did not conduct comprehensive enough literature retrieval strategies, did not provide lists of excluded studies

Table 1 Characteristics of included meta-analysis

Author	Year	Number of primary studies	Number of participants	Quality assessment methods	Number of subgroups	Detailed subgroups	Level of evidence
Choi	2020	15	61787	MINORS	8	2–9	Weak
Tseng	2020	31	119053	NOS, GRADE	23	1–4, 7–25	Non-significant
Dave	2021	14	263947	QUIPS, GRADE	1	4	Weak
Cheung	2020	13	85008	NOS	8	2, 4, 7, 8, 10, 11, 14, 15	Suggestive
Gu	2020	11	70864	NOS	4	2, 3, 9, 10	Convincing
Yuan	2021	13	80202	NOS	16	1–8, 10, 11, 14, 15, 20, 21, 26, 27	Non-significant
Li	2020	32	78136	Cochrane collaboration tool for RCTs, NOS, GRADE	9	1, 7, 8, 10, 22, 23, 28–30	Non-significant
Yuan	2022	24	109865	NOS	16	1, 3, 4, 7, 8, 10–17, 26, 27, 31	Suggestive
Liu	2020	7	25785	NOS	1	3	Weak
Shao	2023	17	90897	NOS, GRADE	2	2, 10	Convincing
Oh	2022	19	57455	NOS	16	1–4, 32–43	Suggestive
Tan	2022	14	24269	NOS	6	3, 4, 10, 14, 20, 21	Suggestive

MINORS methodological index for non-randomized studies score, *NOS* newcastle–ottawa quality assessment scale, *GRADE* grading of recommendations assessment, development and evaluation, *QUIPS* quality in prognosis studies tool, *PSM* propensity score matching, *NA* nucleos(t)ide analogue

1, unadjusted results; 2, results adjusted by multivariable analysis; 3, PSM; 4, cirrhosis; 5, inclusion of decompensated cirrhosis; 6, exclusion of decompensated cirrhosis; 7, Asia studies; 8, non-Asia studies; 9, death or liver transplantation; 10, NA treatment-naïve; 11, non-cirrhosis; 12, follow-up difference less than 1 year for both drugs; 13, follow-up time 1 year or longer for entecavir; 14, clinical cohorts; 15, electronic database records; 16, full length article; 17, abstract; 18, time of enrolment: before 2011; 19, time of enrolment: after and in 2011; 20, multicenter study; 21, single center study; 22, no industry funding; 23, funded by industry; 24, prospective study; 25, retrospective study; 26, follow-up time ≥ 4 years; 27, follow-up time < 4 years; 28, follow-up time ≥ 3 years; 29, cirrhosis patients accounts for 1%-30%; 30, cirrhosis patients accounts for 31%-100%; 31, NA treatment-experienced; 32, treatment duration less than 6 months; 33, treatment duration less than 12 months; 34, exclusion of patients diagnosed with HCC within 6 months; 35, exclusion of patients diagnosed with HCC within 12 months; 36, interval > 3 years in the start point of patient enrolment; 37, interval < 3 years in the start point of patient enrolment; 38, exclusion of patients with baseline HBV DNA levels of < 2000 IU/mL; 39, inclusion of patients with baseline HBV DNA levels of < 2000 IU/mL; 40, exclusion of patients with significant alcoholic liver disease; 41, inclusion of patients with significant alcoholic liver disease; 42, exclusion of patients with CKD or baseline creatinine > 1.5 mg/dL; 43, inclusion of patients with CKD or baseline creatinine > 1.5 mg/dL

and reasons, and did not explain the selection of the primary study designs for inclusion in the review.

Quality of evidence in meta-analyses

Only four meta-analyses (Shao et al. 2023; Tseng et al. 2020; Dave et al. 2021; Li et al. 2020) assessed the quality of evidence on outcome-level via the GRADE approach and provided specific evaluation criteria in the relevant supplementary materials. Given that all the primary studies included in the meta-analyses were observational, we conservatively attributed certainty of evidence to the low level.

Primary study overlap

The group without covariate adjustment, adjusted by the multivariable analysis, adjusted by PSM, NA treatment-naïve subgroups, and cirrhotic patients were the most frequently mentioned in the published systematic reviews. So, we analyzed the overlap of these subgroups. The CCA represented the primary study overlap and was rated very high for all subgroups (Table 2), indicating that some primary studies have been included multiple times in the meta-analyses published up to now. A citation matrix including the visual demonstration of the amount of overlap was provided in (Table 3).

Table 2 Overview of CCA score as measure of primary study overlap

Subgroups	k	CCA	Overlap
Unadjusted results	5	0.38	Very high
Adjusted by multivariable analysis	8	0.27	Very high
PSM	8	0.42	Very high
NA treatment-naïve	7	0.32	Very high
Cirrhosis	7	0.30	Very high

k = number meta-analyses

CCA corrected covered area

Table 3 A citation matrix including the visual demonstration of the amount of overlap

		Tseng (2020)	Yuan (2021)	Li (2020)	Yuan (2022)	Oh et al. (2022)
Chang et al. (2021)	1				1	
Chen et al. (2020)	2				1	1
Cho et al. (2018)	4			1	1	1
Choi et al. (2019)	5		1	1	1	1
Gordon et al. (2019)	6			1		1
Güzelbulut et al. (2021)	7				1	
Ha et al. (2020a)	9		1		1	1
Ha et al. (2020b)	10		1		1	1
Hsu et al. (2020)	11	1	1	1	1	1
Hu et al. (2020)	12					1
Kim et al. (2018a)	13	1	1		1	1
Kim et al. (2019a)	14	1	1	1	1	1
Kim et al. (2019b)	15				1	
Kim et al.(2018b)	16			1		
Kramer et al. (2015)	17			1	1	
Lee et al. (2019)	18	1		1	1	1
Lee et al. (2021)	19				1	
Lee et al. (2020)	20	1	1		1	
Na et al. (2021)	21				1	1
Oh et al. (2020)	22	1	1		1	1
Papatheodoridis GV (2020)	23		1		1	
Pol (2019)	24	1				
Pol and ANRS/AFEF study group (2021)	25				1	
Shin et al. (2021)	26		1		1	1
Su et al.(2020)	27	1	1		1	
Tsai et al. (2017)	28			1		1
Wu et al. (2017)	29			1		1
Yip et al. (2020)	30	1	1		1	1
Yu et al.(2018)	31	1		1	1	1
Yu et al. (2019)	32					1
Studies (k)	32	10	12	13	23	19
		Times studies appeared in reviews	Number of rows	Number of reviews	Proporation	Percentage
		N	*r*	*c*		
	Overall	75	30	5	0.375	37.5%

Preventive effects on HCC

HCC risk in the overall cohort

As shown in Fig. 2A, the overall effect from 35 primary studies showed that TDF was associated significantly with a lower HCC incidence than ETV (HR 0.80; 95% CI 0.75–0.86; $p < 0.05$) with low heterogeneity ($I^2 = 33.5\%$). We then aggerated 19 results adjusted by PSM and found that TDF treatment is associated with lower HCC risk compared to ETV (HR 0.81; 95% CI 0.71–0.93; $p < 0.05$) with $I^2 = 51.7\%$ (Fig. 2B).

HCC risk in specific patients' group

Comparisons between the two drugs in specific CHB patients were shown in Fig. 3. Twenty-seven primary studies investigating the preventive effects of these two drugs on HCC in NA treatment-naïve CHB patients were included. The overall synthesis of these effect sizes resulted in an HR of 0.78 (95% CI 0.68–0.88, $p < 0.05$), which means TDF was associated with significantly lower HCC risk compared with ETV.

Nineteen primary studies reported the pooled effect sizes for HCC risk of liver cirrhosis patients receiving TDF

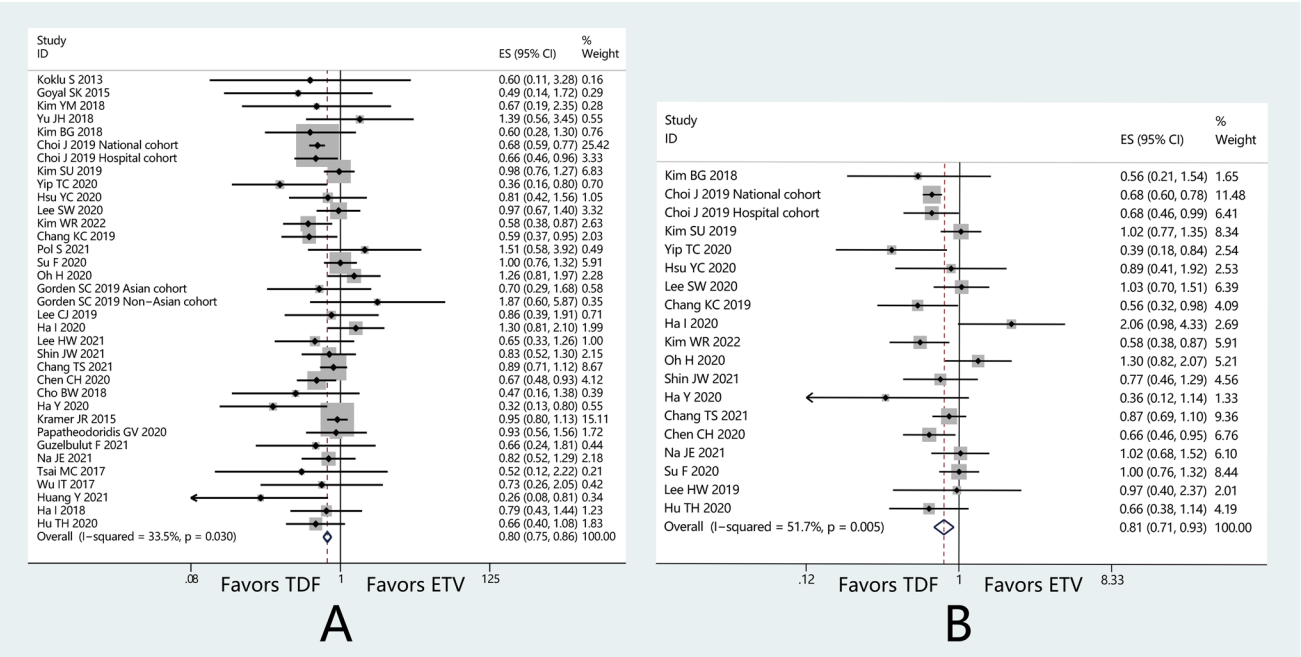

Fig. 2 Forest plot of HCC incidence between TDF and ETV treatment in the overall cohort. **A** results adjusted by multivariable analysis; **B** results adjusted by PSM. *HCC* hepatocellular carcinoma, *TDF* tenofovir disoproxil fumarate, *ETV* entecavir, *CHB* chronic hepatitis B

treatment compared with ETV. We summarized these results and found that the HCC incidence was significantly lower in patients receiving TDF treatment (HR 0.74; 95% CI 0.67–0.82, $p < 0.05$).

Ten primary studies comparing the HCC risk of these two drugs in patients without liver cirrhosis were included in our analysis. Among non-cirrhotic patients, there is no significant difference in the incidence of HCC between TDF treatment and ETV treatment (HR 0.96; 95% CI 0.69–1.33; $p = 0.80$).

In the subgroup analysis based on whether including patients with decompensated cirrhosis, we concluded nine primary studies including patients with decompensated cirrhosis and found that TDF showed a significantly lower risk of HCC over ETV (HR 0.69; 95% CI 0.55–0.85; $P < 0.05$). For the six primary studies excluding patients with decompensated cirrhosis, the pooled results exhibited that there was no difference in the incidence of HCC between the two drugs (HR 0.90; 95% CI, 0.76–1.06; $p = 0.20$).

For analysis concerning regions, twenty-four primary studies from the East tended to favor TDF over ETV against HCC incidence (HR 0.76; 95% CI 0.70–0.83; $p < 0.05$), whereas the eight studies from the West did not (HR 0.93; 95% CI 0.81–1.05; $p = 0.30$).

In the subgroup analysis based on data sources, we pooled the results from twenty-two primary studies using clinical records and found that TDF had a lower risk for HCC than ETV among hospital-based clinical cohorts (HR 0.88; 95% CI 0.80–0.96; $p < 0.05$). For the five primary studies using electronic database records, the results were consistent with those from the clinical cohort (HR 0.74; 95% CI 0.59–0.93; $p < 0.05$).

In terms of follow-up time, existing meta-analyses have not reached a consensus on grouping criteria. Ten primary studies offered the results in patients who received ETV and had a follow-up time at least 1 year longer than those who received TDF. The pooled data showed that TDF was consistently and significantly associated with a lower risk of HCC (HR 0.71, 95% CI 0.64–0.79; $p < 0.05$). Whereas, no difference was observed among the fifteen studies with minimal (< 1 year) disparity in follow-up duration (HR 0.92, 95% CI 0.84–1.02; $p = 0.18$). Besides, no significant difference in risk reduction of HCC was found between TDF and ETV groups in patients with follow-up time ≥ 4 years (HR 0.99; 95% CI 0.84–1.16, $p = 0.74$), while TDF was found to be associated with a reduced risk of HCC than ETV in studies with follow-up length of < 4 years (HR 0.73; 95% CI 0.65–0.82; $p < 0.05$). For the twelve primary studies with follow-up time ≥ 3 years, pooled data showed a similar incidence rate of HCC between the two drugs (HR 0.86; 95% CI 0.70–1.06).

In the aspect of enrollment time, pooled results from eleven or three primary studies showed that TDF and ETV treatment were similar in HCC incidence regardless of whether the time of enrollment was before (HR 0.87; 95% CI 0.86–1.10) or after 2011 (HR 0.93; 95% CI

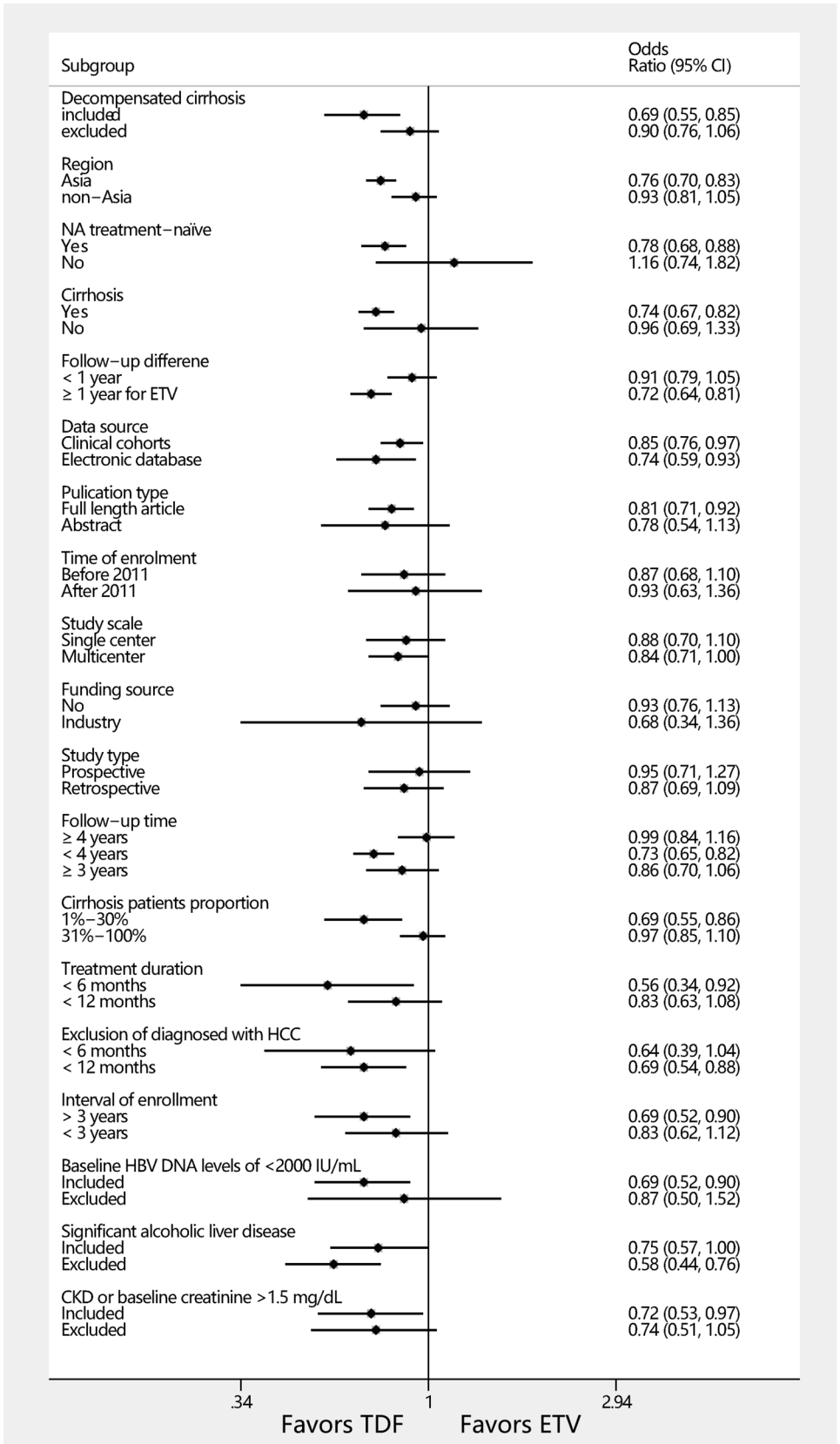

Fig. 3 Summary of pooled HR for HCC incidence between TDF and ETV treatment in different subgroups of CHB patients. *HR* hazard ratio, *HCC* hepatocellular carcinoma, *TDF* tenofovir disoproxil fumarate, *ETV* entecavir, *CHB* chronic hepatitis B

0.63–1.36). Furthermore, pooled results from thirteen primary studies showed that an interval of over three years in the start points of patient enrolment between the two groups resulted in a lower risk of HCC development in the TDF group than in the ETV group (HR 0.69; 95% CI 0.51–0.92; $p < 0.05$). However, the results from five primary studies with enrollment interval between the two groups of less than three years did not support this point (HR 0.83; 95% CI 0.62–1.12).

In the remaining subgroup analysis, the pooled results from primary studies tended to favor TDF over ETV against HCC incidence in the group excluding patients with significant alcoholic liver disease (HR 0.58; 95% CI 0.44–0.76; $p < 0.05$) or diagnosed with HCC within 12 months (HR 0.69; 95% CI 0.54–0.88; $p < 0.05$), accepting treatment less than 6 months (HR 0.56; 95% CI 0.34–0.92; $p < 0.05$), including patients with baseline HBV DNA levels of < 2000 IU/mL (HR 0.69; 95% CI 0.52–0.90; $p < 0.05$), and including patients with CKD or baseline creatinine > 1.5 mg/dL (HR 0.72; 95% CI 0.53–0.97; $p < 0.05$). However, the two drugs seemed to be similar in the subgroup stratified by publication type (full-text articles or meeting abstracts), study scale (multicenter or single center), funding source (with or without industry funding), and study type (prospective or retrospective).

Death or transplantation incidence

Fifteen primary studies reported incidences of death or transplantation. As shown in Fig. 4, the pooled result indicated that TDF treatment was associated with a significantly lower rate of death or liver transplantation caused by CHB compared with ETV treatment (HR 0.89; 95% CI 0.80–0.99; $P < 0.05$) without significant between-study heterogeneity ($I^2 = 0\%$).

Publication bias

Funnel plots were constructed to estimate the extent of publication bias in the pooled analyses (Supplementary Fig. S1). No apparent publication bias was shown among the results. We did not test publication bias for the remaining subgroups not presented in Supplementary Fig. S1 because too few primary studies were available to perform a valid statistical test.

Discussion

In clinical medical practice, systematic reviews become commonplace partly because of the continuous output of clinical research results (Pollock et al. 2023). In turn, the rapidly increasing number of systematic reviews has led many to perform reviews of these reviews, which were variously known as "overviews", "umbrella reviews", or

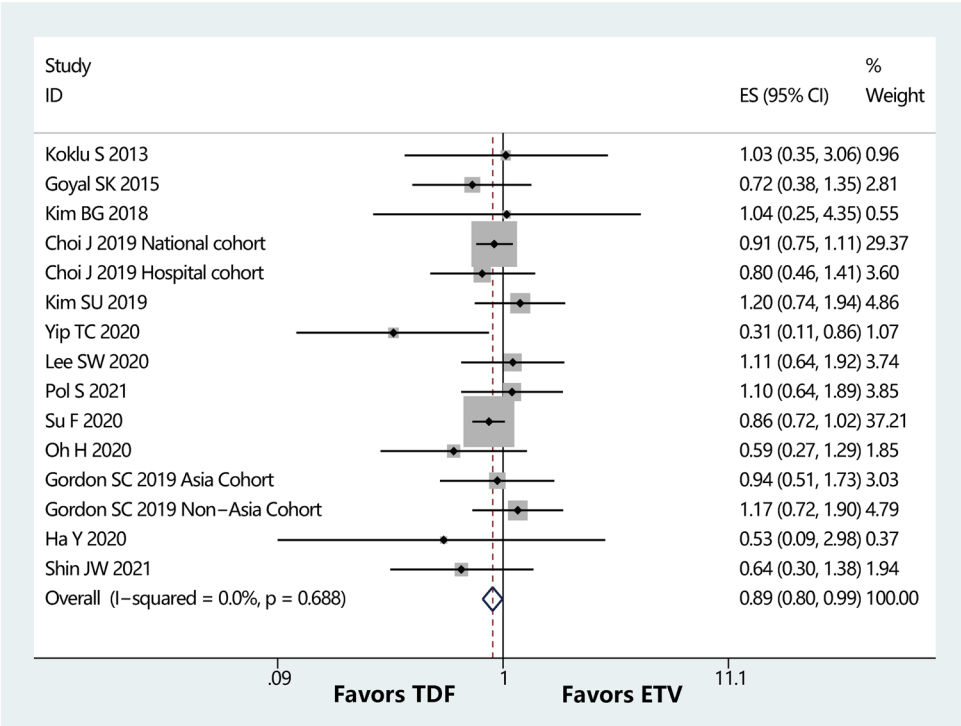

Fig. 4 Pooled HR for death or liver transplantation incidence between TDF and ETV treatment in CHB patients. *HR* hazard ratio, *TDF* tenofovir disoproxil fumarate, *ETV* entecavir, *CHB* chronic hepatitis B

"reviews of reviews", trying to discover and obtain the best evidence of a certain territory.

The HCC risk of receiving TDF compared with ETV treatment in CHB patients with different baseline characteristics such as NA-naïve, cirrhosis, and different regions has been examined in many published meta-analyses. This umbrella review provided an overview of the latest meta-analytical evidence on the risk of developing HCC in CHB patients receiving TDF versus ETV treatment. As no previous research has examined the literature in this way, this is the first and most comprehensive umbrella review that critically reviews the prevention effect on HCC of the two drugs before the present study, as well as evaluates the methodological quality of the meta-analyses and quality of evidence. To ensure a high scientific standard, we followed the latest recommendations from the Cochrane Collaboration (Pollock et al. 2023) for reporting an umbrella review. In addition to the narrative summary of specific characteristics of the different meta-analyses, we aggregated the current evidence on a quantitative level and conducted meta-analyses. These kinds of analyses reveal variation between results from individual meta-analyses and may thus contribute to explaining observed heterogeneity between results from individual meta-analyses. Our goal is to simplify knowledgeable clinical decisions when choosing the drug for a certain type of CHB patients to improve their disease-related outcomes.

We compared the differences in the preventive effect of TDF versus ETV on HCC among the overall cohort and 43 specific subgroups of CHB patients, as well as differences in the death or transplantation rate in the overall cohort. We found that TDF treatment was associated with a lower incidence of HCC, which was consistent with several previous researches (Choi et al. 2021; Cheung et al. 2020; Gu et al. 2020; Shao et al. 2023; Liu et al. 2020; Tan et al. 2022). However, some other researchers (Tseng et al. 2020; Dave et al. 2021; Li et al. 2020) believed that there was no significant difference in the incidence of HCC between receiving these two drugs.

As is well known, liver cirrhosis is an important risk factor for HCC (Persson et al. 2012). A multicenter cohort study (Papatheodoridis et al. 2017) found that the annual incidence of HCC differed significantly within and beyond the first 5 years of NA treatment in patients with cirrhosis but not in those without, indicating a possible interaction between NA treatment and cirrhosis. Subgroup analysis based on the criteria of whether or not including patients with decompensated cirrhosis in a primary study showed a statistically significant or insignificant difference in HCC incidence between the two drugs. Three relatively large-scale cohort studies (Kim et al. 2018, 2019; Lee et al. 2020) from Korea excluded patients with decompensated cirrhosis, whereas another study (Choi et al. 2019) included those patients. Only a few meta-analyses authors (Choi et al. 2021; Yuan et al. 2021) have noticed this difference in the inclusion criteria of primary studies and discussed it in their study. This point may be a plausible explanation for the inconsistent results of previous studies. However, the study by Yuan et al. showed the similarity of TDF to ETV in HCC prevention persisted in two subgroups including or excluding decompensated cirrhosis patients. This may be related to the insufficient sample size of their research. Hence, more studies with a large sample size are needed to clarify this issue.

Our study showed that in the Asian study, patients treated with TDF showed a lower incidence of HCC, while in the non-Asian study, patients treated with the two drugs showed a similar HCC risk. However, the specific mechanism underlying this regional discrepancy remained unclear. Possible reasons might include differences in ethnicity, HBV genotypes, health care system, as well as baseline characteristics (Tian and Jia 2016; Mittal et al. 2018; Robinson et al. 2019). Most of the included primary studies only analyzed Asian patients with CHB, where HBV genotype C prevails among chronic carriers (Bae et al. 2005). It has been confirmed that genotype C confers higher HCC risk than others (Yang et al. 2008). In addition, the transmission mode of HBV varies among patients in different regions. In Asians with CHB, vertical HBV transmission from mother to child predominates, while HBV is usually transmitted during childhood and adulthood in Europeans and Americans with CHB[1], which may lead to a lower HCC risk. A recent study by Jang et al. (Jang et al. 2022) found higher HBeAg positivity and liver cirrhosis proportion among Koreans than Caucasians.

The later approval and availability of TDF for the treatment of CHB might partly explain the result from studies in which the follow-up time was shorter by 1 year or more in patients receiving TDF compared with ETV. TDF was not approved to treat CHB until 2008 in the USA and 2011 in East Asia, whereas ETV had been available since 2005 (EASL 2017; Terrault et al. 2018). This asynchronous introduction of the two drugs could have resulted in physicians prescribing ETV to the patient populations bearing higher potential HCC risks (Shao et al. 2023). For example, owing to the later approval of TDF, physicians may preferentially prescribe ETV to patients with more severe liver disease because they would have met the treatment indications before TDF became available (Tseng et al. 2020). The follow-up duration of TDF-treated patients was usually shorter than ETV-treated ones in real-world studies. With longer observation time, more HCC events might occur in ETV-treated patients, which may mislead to the superiority of TDF over ETV in reducing the HCC risk observed in previous meta-analyses. Our subgroup analysis showed that TDF-treated and ETV-treated patients had similar HCC

incidence when follow-up duration was longer than 4 years in both groups, which may be a hint that HCC events were likely to occur in CHB patients over a longer observation period regardless of the therapeutic agent. Moreover, the wild application of TDF was delayed in Asian countries because of reimbursement policies. For instance, since its initial introduction to Hong Kong in 2012, TDF was restricted to only patients with antiviral resistance or young female patients of childbearing age, which is younger than most patients with CHB receiving antiviral treatment, and remained more restricted in use than ETV until 2017 (Kim et al. 2019; Ma et al. 2019; Drafting Committee for Hepatitis Management Guidelines 2019).

In a 12-year follow-up cohort study (Papatheodoridis et al. 2020), researchers found a significant difference in the incidence of HCC in NA-naïve and NA-experienced patients, which suggested that previous NA therapy may be one of the confounding factors leading to different potential HCC risks in CHB patients before receiving subsequent ETV or TDF treatment. Combined with the results that TDF treatment was related to a lower risk of HCC in cohorts of cirrhosis patients or cohorts including patients with decompensated cirrhosis in our study, the superiority of TDF over ETV therapy on the incidence of HCC may be observed only in CHB patients at higher HCC risk such as cases from Asian, NA-naïve or with cirrhosis, but not in patients at lower HCC risk such as Europeans and Americans, NA-experienced or without cirrhosis (Lee et al. 2021).

In existing meta-analyses, authors usually chose multivariable analysis or PSM to adjust for confounding factors in CHB patients' baseline characteristics. Nevertheless, using PSM and covariate-adjusted estimates did not guarantee that the results in the previous meta-analyses were robust because only a few primary study authors have provided a detailed list of the variables, even so, we still found that some key variables were omitted. For example, in the study by Kim et al. (Kim et al. 2019) only 9 variables were used for matching, and well-known predictors of HCC, such as HBV DNA levels and alanine aminotransferase levels, were not included. Wu et al. (Wu et al. 2017) did not adjust for variables such as gender, alanine aminotransferase and aspartate aminotransferase levels. Hsu et al. (Hsu et al. 2020) did not adjust the creatinine levels of included CHB patients. This issue was particular in studies using data from electronic databases, where clinical data on key covariates may not be available, meaning that resulting adjusted estimates may still be biased in an unpredictable direction (Choi et al. 2022). Besides, we found a significantly lower HCC risk in the TDF group when patients with alcoholic liver disease were excluded. The time of being diagnosed with HCC was also crucial, and some primary studies excluded CHB patients who developed HCC within six months after enrollment. It has been reported that the tumor volume doubling time (TVDT) of HCC is approximately 4–5 months (Nathani et al. 2021). Therefore, it is difficult to exclude patients with HCC present at the start of treatment by excluding patients who develop HCC within six months. However, these variables have generally not been given sufficient attention in existing studies.

In principle, researchers should conceive appropriate exclusion criteria to filter out studies in considerably heterogeneous populations. However, researchers may prefer to use relatively loose inclusion criteria to maximize sample size and assess the effects of heterogeneity through subgroup analyses. However, such subgroup analyses remain subject to uncertainty. When conducting subgroup analysis based on a certain factor, the distribution of other factors among subgroups may not be uniform. For example, when comparing the subgroups of patients with liver cirrhosis versus those without, the proportion of primary studies that only included NA-naïve patients differed between each subgroup. In a meta-analysis by Tseng et al., the 3 industry-funded studies had lower HR than the 11 non-industry-funded studies (Tseng et al. 2020). However, 2 of the 3 industry-funded studies were based on electronic databases, which may themselves be associated with lower HR, thus the subgroup analysis examining the effect of funding may be confounded by differences in the data source (Sapena et al. 2022).

One key challenge in conducting an umbrella review was how to deal with study overlap across different meta-analyses, as the same primary study may be included in multiple meta-analyses. However, authors often disregard overlaps rather than address the issue in their work, which may lead to unreliable conclusions. Pieper et al. (Pieper et al. 2014) argued that all producers of overviews should analyze the overlaps and report their analysis.

Our study reported the overlap of primary studies in existing meta-analyses for the first time. The results of the citation matrix and CCA showed that there was a high degree of overlap in the subgroups of confounding factors unadjusted cohort, adjusted by multivariable analysis cohort, PSM cohort, NA treatment-naïve patients, and liver cirrhosis patients, indicating that some primary studies have been repeatedly included in different published meta-analyses. Future meta-analyses authors should conduct broad searches to screen out updated primary studies, rather than conducting repeated analyses of these that have already been included multiple times. Applying advanced meta-analytic methods such as individual participant-data (IPD) meta-analysis is also an advisable choice, which would offer a more robust estimate, by allowing biases to be explicitly accounted for with consistent methodologies across all datasets (Choi et al. 2022). However, an IPD meta-analysis would not address the potential lack of universality resulting from the predominance of studies conducted in East Asia.

There are several limitations of our study. This umbrella review was based on evidence from published systematic reviews and meta-analyses, thus, our conclusions may be similar to some of the included studies. Meanwhile, potential limitations and shortcomings of the included studies can be inherent to the study design and might undermine the validity of the findings. Only four of the meta-analyses included in this overview adopted the GRADE approach to evaluate the evidence quality. According to the AMSTAR 2 tool, not all of the included systematic reviews were rated as high quality. The use of an umbrella review brought the risk of duplicating the findings from the included studies. Despite this, our study demonstrated notable strengths, such as rigorous methodological approaches, extensive database search, and comprehensive analysis.

In conclusion, our umbrella review provided recommendations for future primary studies and meta-analyses comparing the efficacy of the two drugs by comprehensively reviewing existing evidence. We found TDF treatment was associated with a lower HCC risk compared with ETV treatment in most subgroups. However, it should be noted that all of the studies that compared the HCC risk between the 2 treatments either favored TDF or showed no differences (Choi and Lim 2019). None of the studies showed results favoring ETV over TDF (Kim et al. 2019). In the current meta-analyses and primary studies, especially for the meta-analyses that included data after confounding factors adjustment, the conclusions of these meta-analyses may not be as robust as their authors claimed due to the heterogeneity of the variables involved in the primary study and the possible absence of certain key variables. In order to compare the preventive effects of these two drugs on HCC more scientifically, our work highlights the need for meta-analyses based on standardized primary studies. Resorting to more advanced meta-analysis methods is also encouraged.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethics approval Ethical approval was waived by the local Ethics Committee of Qilu Hospital of Shandong University in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

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