JHEP|Reports

Comment on "Lower incidence of hepatocellular carcinoma with tenofovir alafenamide in chronic hepatitis B: Evidence from a large-scale cohort"

To the Editor:

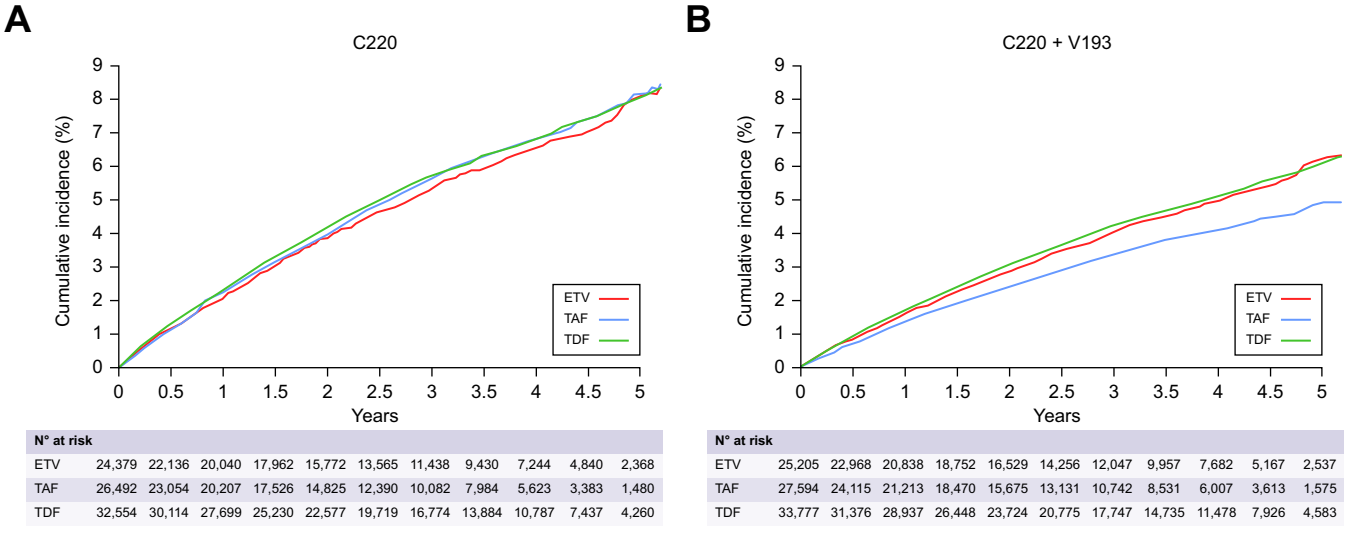
We read with great interest the recent study by Hye-Jin Yoo *et al.* published in the *Journal.*[1] Determining which antiviral agent results in better clinical outcomes, including the incidence of hepatocellular carcinoma (HCC), in patients with chronic hepatitis B, is a significant and intriguing topic. However, when interpreting big data studies using claims data, several limitations must be carefully considered.

First, regarding the operational definition of HCC diagnosis, relying solely on ICD-10 codes to assess HCC incidence may lead to an overestimation of the actual incidence rate. In South Korea, the V193 code is also used when diagnosing cancer to provide medical expense benefits. This code helps distinguish patients with confirmed HCC from those without. The current study does not appear to have incorporated the V193 code, which may have resulted in an overestimation of HCC incidence. We used South Korea's HIRA data to compare the incidence of HCC among patients who initiated treatment with entecavir (ETV), tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF) after November 2017, based on the C220 and C220 + V193 criteria. Our analysis revealed that the incidence rates of HCC varied depending on the application of the V193 code (Fig. 1).

When HCC was diagnosed using only the C220 code, the incidence rates were 1.83 (95% CI 1.78–1.89) per 100 person-years in the overall cohort, 1.78 (95% CI 1.66–1.88) per 100 person-years in the ETV group, 1.87 (95% CI 1.77–1.98) per 100 person-years in the TAF group, and 1.84 (95% CI 1.76–1.93) per 100 person-years in the TDF group. However, when both C220 and V193 codes were applied for HCC diagnosis, the incidence rates were 1.27 (95% CI 1.23–1.32) per 100 person-years in the overall cohort, 1.32 (95% CI 1.24–1.41) per 100 person-years in the ETV group, 1.10 (95% CI 1.02–1.18) per 100 person-years in the TAF group, and 1.36 (95% CI 1.29–1.43) per 100 person-years in the TDF group. Studies in South Korea using hospital-based cohorts have found HCC incidence rates ranging from 0.96–1.40 per 100 person-years, despite including a higher proportion of patients with cirrhosis (33–47%) than in the current study (19.9%).[2,3]

The second important consideration is that this study included patients with decompensated cirrhosis in the analysis. The study focused on patients who underwent antiviral therapy after January 2018, enrolling participants only after TAF became available in South Korea (November 2017) to ensure comparability under similar conditions. However, in South Korea, TAF was not initially reimbursed for patients with decompensated cirrhosis. As of March 2021, TAF was made available only for a specific subset of patients with decompensated cirrhosis, such as those with renal impairment or osteoporosis. The inclusion of patients with decompensated cirrhosis in the analysis may have led to differences in baseline characteristics between groups, despite using propensity score matching.

In conclusion, HIRA data, as a type of big data, holds substantial power and provides valuable clinical insights. However, researchers must be cautious as results may vary depending



N° at risk												
ETV	24,379	22,136	20,040	17,962	15,772	13,565	11,438	9,430	7,244	4,840	2,368	
TAF	26,492	23,054	20,207	17,526	14,825	12,390	10,082	7,984	5,623	3,383	1,480	
TDF	32,554	30,114	27,699	25,230	22,577	19,719	16,774	13,884	10,787	7,437	4,260	

N° at risk												
ETV	25,205	22,968	20,838	18,752	16,529	14,256	12,047	9,957	7,682	5,167	2,537	
TAF	27,594	24,115	21,213	18,470	15,675	13,131	10,742	8,531	6,007	3,613	1,575	
TDF	33,777	31,376	28,937	26,448	23,724	20,775	17,747	14,735	11,478	7,926	4,583	

Fig. 1. Kaplan-Meier analysis of cumulative HCC incidence according to the operational definition of HCC diagnosis: (A) Diagnosis based on C220; (B) Diagnosis based on the combination of C220 and V193. HCC, hepatocellular carcinoma.

on the operational definitions used. Findings from big data studies should be interpreted carefully. Furthermore, additional support from research datasets, such as hospital cohorts that enable a more detailed analysis of patient data, is essential for validating and improving these insights.

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Conflict of interest

The authors declare no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: SSK, GHS. Data analysis: GHS, Writing of the first draft of the manuscript: JH, SSK. All authors reviewed and approved the manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2025.101334.

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Author names in bold designate shared co-first authorship

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