Finally, and in contrast with our study, the authors did not find a significant association between antibiotic resistance and mortality. However, the retrospective nature of the Portuguese study limits its capacity to adequately address this issue, very well demonstrated in large scale studies published recently.[1,3]

Our study and the data reported in the letter by Morais *et al.*, demand the urgent evaluation of new strategies aimed at preventing the spread of antibiotic resistance in the cirrhotic population, including epidemiological surveillance and antibiotic stewardship programs and rapid microbiological tests.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.07.001.

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M. Hernández-Tejero[1]
M. Triolo[1]
J. Fernández[1,2,3,*]
[1]*Liver ICU, Liver Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain*
[2]*European Foundation of Chronic Liver Failure (EF-Clif), Barcelona, Spain*
[3]*Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHED), ISCIII, Spain*
*Corresponding author. Address: Liver Unit, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain.
Tel.: +34-93-2275400 3329, fax: +34-93-4515522.
E-mail address: jfdez@clinic.cat

Comparison of risk of hepatocellular carcinoma between tenofovir and entecavir: One direction or no direction

To the Editor:

We read with interest the study by Kim *et al.* that was recently published in the *Journal of Hepatology*.[1] The authors concluded that the risk of hepatocellular carcinoma (HCC) did not differ between patients treated with entecavir (ETV) and those treated with tenofovir disoproxil fumarate (TDF). This seems to contradict our earlier publication, which showed a lower risk of HCC with TDF than with ETV.[2] The contradicting results should be interpreted with caution, taking into account differences in the characteristics of the study population, study design, statistical power, and potential confounding.

The most prominent difference between the 2 studies is the number of patients with cirrhosis included in the analyses. Although the 2 studies applied a similar definition for cirrhosis (image diagnosis or platelet count, <150,000/μl), cirrhosis was more prevalent in our study population (58.8%) than in that of Kim *et al.* (31.4%). The number of patients included in the propensity score-matched analysis was greater in our study (510 *vs.* 380 pairs). Furthermore, the mean baseline hepatitis B virus (HBV) DNA levels were higher in our study (6.6 *vs.* 5.6 $\log_{10}$ IU/ml). Lastly, patients with decompensated cirrhosis were included in our study but excluded in the study of Kim *et al.* All these factors indicate that the patients in our study had a higher risk of developing HCC than those in the study by Kim *et al.* We are particularly curious why the authors excluded patients with decompensated cirrhosis in their analysis. It is already well known that hepatic decompensation is reversible in most patients by treatment with ETV or TDF.[3,4] Patients with decompensated cirrhosis have the highest risk of HCC, which may increase the statistical power of the analyses greatly. It is obvious that with insufficient statistical power, a significant difference in HCC incidence could not be identified between the 2 treatments.

Another important issue to be raised is the consideration of treatment modification during follow-up. In our study, treatment was modified in 11.7% of patients in the ETV group, mostly to TDF, during follow-up because of incomplete viral suppression (HBV DNA level, ≥100 IU/ml), virological breakthrough, or drug resistance. We censored the patients at 6 months after the treatment modification. However, Kim, *et al.* did not report the rate of treatment modification in their study, and it seems that the factor was not adjusted in their analyses. If TDF confers a lower risk of HCC than ETV, the patients in the ETV group with treatment modification from ETV to TDF during follow-up may have a reduced risk of HCC, consequently diluting the statistically significant difference in HCC risk between the 2 original groups.

We also have a concern about the propensity score-matched analysis in the study of Kim *et al.* They used only 9 variables for the matching, and well-known predictors of HCC, such as HBV DNA levels, alanine aminotransferase levels, and international normalized ratio, were not included in the matching for an unreported reason, despite the availability of data. As many variables are included in the matching process, the risk of confounding can be minimized, and we used 16 matching variables in our study.

The annual incidence of HCC in patients with chronic HBV infection ranges from 0.2% to 1% without cirrhosis and from 1% to 5% with cirrhosis. Comparative effectiveness research that compares these rare outcomes requires sufficient numbers of

patients and outcome events to ensure statistical power. Showing non-significance in clinical outcomes between the 2 treatments is easier than identifying statistically significant differences in comparative effectiveness research.[5] This may explain why many previous studies, including the study of Kim *et al.*, have shown no significant difference in risk of HCC among drugs.[1,6–8]

Collectively, it is important to note that all the studies that compared the risk of HCC between TDF and ETV therapies have indicated one direction favoring TDF or no direction. No study has shown the opposite direction of favoring ETV over TDF.[6–8] Even the study by Kim *et al.* also indicated a lower risk of HCC with TDF in patients with cirrhosis (hazard ratio 0.85; HCC incidence at 5 years of treatment, 16.0% with TDF *vs.* 20.9% with ETV), although the difference was not statistically significant. A meta-analysis consisting of 7 studies (3,698 patients) reported a lower incidence of HCC in patients with TDF than in those with ETV.[9] Recently, another large historical cohort study from Hong Kong showed a significantly lower risk of HCC in TDF than in ETV.[10]

Given that a randomized clinical trial, which is the optimum for this topic, cannot be conducted in the future, we have to depend heavily on the results of observational studies. Accordingly, caution is required in interpreting the results from observational studies, considering whether they have sufficient numbers of patients and outcome events, with high internal validity in study design and analysis.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.06.013.

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Author names in bold designate shared co-first authorship

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Jonggi Choi[1]
Young-Suk Lim[1,*]
[1]*Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Republic of Korea*
*Corresponding author. Address. Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea. Tel.: +82 02 3010 5933, fax: +82 02 485 5782.
E-mail address: limys@amc.seoul.kr

Reply to: "Comparison of risk of hepatocellular carcinoma between tenofovir and entecavir: One direction or no direction"

To the Editor:

First of all, we greatly appreciate the letter from Choi *et al.*[1] regarding our study,[2] where we concluded that the risk of hepatocellular carcinoma (HCC) was not statistically different between patients treated with entecavir (ETV) and those treated with tenofovir disoproxil fumarate (TDF) for chronic hepatitis B virus (HBV) infection. Our conclusion seems to contradict the earlier publication by Choi *et al.*,[3] which indicates a significantly lower risk of HCC among the TDF group compared to the ETV group. Indeed, since the publication of the study by Choi *et al.*,[3] the controversy surrounding which antiviral agent is better in terms of reducing HCC risk has become heated. Most recently, in the International Liver Congress™, Vienna, Austria in April 2019, 2 studies based upon cohorts from the Republic of Korea and from the United States of America were published, both of which indicate that the risk of HCC is not statistically different between the 2 treatment groups.[4,5] However, simultaneously, Yip *et al.*[6] showed that the 5-year cumulative incidence of HCC was lower in the TDF group compared to the ETV group (1.2% *vs.* 2.3%).

As indicated by Choi *et al.*,[1] patients with decompensated cirrhosis were not included in our study. We also acknowledge that decompensated cirrhosis is a well-known risk factor of HCC development. However, the major end point of this study