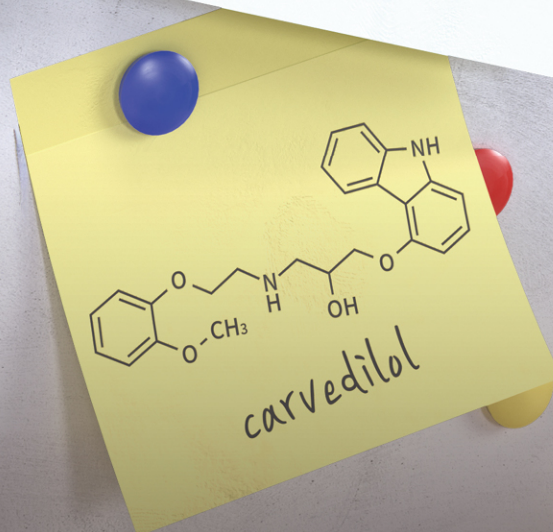


# CLINICAL and MOLECULAR HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases



## Non-invasive Model guiding Carvedilol for Clinically Significant Portal HTN

Inpatient variability of tacrolimus on CKD in LT  
HCV self-testing and disease burden reduction  
MASLD and microbiota  
Bariatric surgery for metabolic cirrhosis



# Chronic hepatitis B, extrahepatic malignancies and the use of antiviral drugs

Meng-Che Wu<sup>1,2,3</sup>, Shih-Chi Yang<sup>4</sup>, and Shuo-Yan Gau<sup>5,6,7</sup>

<sup>1</sup>Division of Pediatric Gastroenterology, Children's Medical Center, Taichung Veterans General Hospital, Taichung; <sup>2</sup>Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung; <sup>3</sup>School of Medicine, Chung Shan Medical University, Taichung; <sup>4</sup>Education Center, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan; <sup>5</sup>Department and Graduate Institute of Business Administration, National Taiwan University, Taipei; <sup>6</sup>Department of Pharmacology, Chung Shan Medical University, Taichung; <sup>7</sup>Orthopedics Department, Chi-Mei Medical Center, Tainan, Taiwan

**Keywords:** Chronic hepatitis B; Extrahepatic malignancy; Antiviral drugs; Real-world study

Dear Editor,

We read with great interest the article by Hur et al., entitled "Extrahepatic malignancies and antiviral drugs for chronic hepatitis B: A nationwide cohort study" published recently in *Clinical and Molecular Hepatology*.<sup>1</sup> The study provides important insights into the long-term risks of extrahepatic malignancies in chronic hepatitis B patients treated with entecavir (ETV) or tenofovir disoproxil fumarate (TDF). We would like to raise some additional methodological concerns that could help strengthen the study's findings.

First, the current use of administrative codes to define the study population of viral hepatitis could lead to potential misclassification bias. While large administrative databases provide valuable population-wide data, reliance on ICD-10-CM coding systems for disease classification can introduce bias in diagnosis definitions,<sup>2</sup> a limitation frequently mentioned in population-based real-world studies.<sup>3,4</sup> A recent validation study has shown that the positive predictive

value (PPV) of ICD-10 codes for hepatitis B and C can be variable and often suboptimal.<sup>5</sup> Lacking precision in diagnostic codes may lead to false-positive diagnoses of hepatitis B and C, potentially influencing the observed relationship between antiviral therapy and cancer risk, and making it challenging to draw accurate conclusions about the comparative effects of ETV and TDF on subsequent malignancies.

The issue of comedication is another important factor that could introduce confounding into the study's findings. Common medications such as aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) have known effects on cancer risk, particularly for gastrointestinal cancers, due to their anti-inflammatory and antithrombotic properties.<sup>6</sup> Aspirin, for instance, has been reported to reduce the risk of esophageal and gastric cancers in real-world observations.<sup>7</sup> Similarly, aside from aspirin and NSAIDs, other common medications, such as statins, which were also reported to be associated with gastric cancer risk reduction, could further complicate the interpretation of results.<sup>8</sup> Given

**Corresponding author :** Shih-Chi Yang

Education Center, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, No.138, Sheng Li Road, Tainan City 704, Taiwan  
Tel: +886 6 235 3535, Fax: +886 6 2766692, E-mail: shihchiyang90@gmail.com  
<https://orcid.org/0009-0003-9837-2813>

**Editor:** Gi-Ae Kim, Kyung Hee University, Korea

**Received :** Oct. 14, 2024 / **Accepted :** Oct. 16, 2024

that in the current study, the detailed profile of comedication use were not provided, readers were not able to determine whether study populations were more likely to be taking medications that could influence cancer risk. To improve the robustness of the findings, future studies were recommended include a detailed profile of cancer-associated comedication status to assess the potential impact of these medications on incident malignancy outcomes.

Lastly, adherence to antiviral therapy was not measured in the study. Poor adherence could lead to poor viral control and potentially increasing the risk of both intrahepatic and extrahepatic malignancies<sup>9</sup>. It would be valuable for future studies to assess adherence by utilizing pharmacy refill data or patient self-reports, which would allow researchers to further examine the potential role of adherence levels and malignancy outcomes.

### Authors' contributions

All the authors involved in drafting or revising the article and approved of the submitted version. Study conception and design: Gau SY, Wu MC, Yang SC. Original draft preparation: Gau SY, Wu MC, Yang SC.

### Conflicts of Interest

The authors have no conflicts to disclose.

## REFERENCES

1. Hur MH, Lee DH, Lee JH, Kim MS, Park J, Shin H, et al. Extrahepatic malignancies and antiviral drugs for chronic hepatitis B: a nationwide cohort study. *Clin Mol Hepatol* 2024;30:500-514.
2. Gau SY. Methotrexate use and liver outcomes in psoriasis and rheumatoid arthritis patients: a commentary on "risk of liver disease in patients with psoriasis, psoriatic arthritis and rheumatoid arthritis receiving methotrexate: a population-based study". *J Am Acad Dermatol* 2021;85:e399-e400.
3. Gau SY, Huang JY, Wei JC. Tramadol use increases mortality and risk of major adverse cardiovascular events in rheumatoid arthritis patients: evidence from a population-based cohort study. *Eur J Prev Cardiol* 2022;29:e237-e238.
4. Huang SC, Gau SY, Huang JY, Wu WJ, Wei JC. Increased risk of hypothyroidism in people with asthma: evidence from a real-world population-based study. *J Clin Med* 2022;11:2776.
5. Sheu MJ, Chin TW, Ku FP, Li CY, Li ST, Lu TH. Validation of coding algorithms for identifying people with viral hepatitis using claims data according to different standard references. *BMC Infect Dis* 2022;22:222.
6. Wong RSY. Role of nonsteroidal anti-inflammatory drugs (NSAIDs) in cancer prevention and cancer promotion. *Adv Pharmacol Sci* 2019;2019:3418975.
7. García Rodríguez LA, Soriano-Gabarró M, Vora P, Cea Soriano L. Low-dose aspirin and risk of gastric and oesophageal cancer: a population-based study in the United Kingdom using The Health Improvement Network. *Int J Cancer* 2020;147:2394-2404.
8. Su CH, Islam MM, Jia G, Wu CC. Statins and the risk of gastric cancer: a systematic review and meta-analysis. *J Clin Med* 2022;11:7180.
9. Allard NL, MacLachlan JH, Dev A, Dwyer J, Srivatsa G, Spelman T, et al. Adherence in chronic hepatitis B: associations between medication possession ratio and adverse viral outcomes. *BMC Gastroenterol* 2020;20:140.

### Abbreviations:

ETV, entecavir; NSAIDs, nonsteroidal anti-inflammatory drugs; PPV, positive predictive value; TDF, tenofovir disoproxil fumarate