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Letters to the editor

Non-hepatic cancers in alcohol-related liver disease with insights for clinical management

Dear Editor,

Alcohol-related liver disease (ALD) is a major global contributor to liver-related morbidity and mortality, with clinical outcomes extending beyond cirrhosis and hepatocellular carcinoma to encompass extrahepatic malignancies, such as lung cancer. In this context, Crockett et al. conducted a biopsy-confirmed, multicenter international cohort study of nearly 700 patients, applying competing risk models to examine the incidence and predictors of non-hepatic cancers (NHC) [1]. They found that NHC occurred more frequently than hepatocellular carcinoma in ALD, with lung and gastrointestinal cancers predominating, and identified age, smoking history, and cirrhosis as independent risk factors. This study highlights an underexplored dimension of ALD and offers novel insights with clear clinical relevance. At the same time, we also note that certain methodological and clinical aspects merit further exploration.

Firstly, it deserves attention that although the authors included variables such as age, smoking status, body mass index, and cirrhosis; several key laboratory parameters and derived scores were not incorporated, including alpha-fetoprotein (AFP) and other tumor markers, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) reflecting liver function, the albumin-bilirubin (ALBI) grade derived from laboratory values, the Eastern Cooperative Oncology Group (ECOG) performance status, etc. These factors are not only closely related to the severity of liver disease but are also widely recognized as important predictors of cancer risk [2,3]. If these key parameters had been included in the analysis, potential confounders might have been more fully controlled, thereby further strengthening the robustness and clinical interpretability of the study's conclusions.

Secondly, the inclusion of patients with pre-existing extrahepatic malignancies may have introduced additional heterogeneity. While these cases were not counted as incident NHC events, their higher risks of recurrence, metastasis, and competing events could influence incidence estimates. A sensitivity analysis excluding or stratifying such patients might further strengthen the robustness and clinical relevance of the findings.

In addition, the study involved patients from multiple countries and centers, where differences in diagnosis, data collection, and follow-up may introduce bias. Without accounting for these center effects—especially in the absence of systematic laboratory data—inter-center variation might affect interpretation. Incorporating center as a random effect or validating results through stratified and sensitivity analyses [4] would better address this issue and yield more representative conclusions on NHC risk in ALD patients.

There is also room for refinement in accounting for follow-up treatments and interventions. In ALD, measures such as alcohol and smoking cessation, antifibrotic therapy, and liver transplantation can substantially alter long-term outcomes and cancer risk [5–7]. Without adjusting for these factors, the results may overestimate incidence or misattribute risk, whereas future studies incorporating them could yield a more accurate risk profile of NHC in ALD patients.

Overall, the study by Crockett et al. broadens our understanding of cancer outcomes in ALD, particularly by revealing the significant incidence and burden of NHC, including lung cancer. We highly commend the authors for their valuable contribution based on a large multicenter cohort. At the same time, further refinements in baseline data, inclusion criteria, control of multicenter heterogeneity, follow-up interventions, and observation duration would make future conclusions more robust and clinically persuasive.

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AI use statement

AI GPT (OpenAI) was used only for grammar and sentence structure checking to ensure compliance with standard English writing conventions.

Declaration of competing interest

None.

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Weiyi Jiang[#]
Department of Oncology, Ningbo Municipal Hospital of Traditional Chinese Medicine (TCM), Affiliated Hospital of Zhejiang Chinese Medical University, Ningbo 315000, China

Qianqian Yin[#]
Department of Rheumatology and Immunolog, Seventh People's Hospital of Shanghai University of Traditional Chinese Medicine, Shanghai 200137, China

Mengyi Hu
Department of Oncology, Ningbo Municipal Hospital of Traditional Chinese Medicine (TCM), Affiliated Hospital of Zhejiang Chinese Medical University, Ningbo 315000, China

Tingsu Zhang[*]
Department of Oncology, Ningbo Municipal Hospital of Traditional Chinese Medicine (TCM), Affiliated Hospital of Zhejiang Chinese Medical University, Ningbo 315000, China

[*]Corresponding author. Department of Oncology, Ningbo Municipal Hospital of Traditional Chinese Medicine (TCM), Affiliated Hospital of Zhejiang Chinese Medical University, Ningbo 315000, China.
E-mail addresses: jiangweiyilwbz@163.com (W. Jiang), qqydeyouxiang@163.com (Q. Yin), nbszyyhmy@163.com (M. Hu), zts20070901@163.com (T. Zhang).

[#] Weiyi Jiang and Qianqian Yin contributed equally to this work.