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Letter to the Editor

The Rising Burden of Hepatocellular Carcinoma: Is the Gender Gap Narrowing?

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Dear Editors,

The landscape of hepatocellular carcinoma (HCC) is continuously evolving. Recent global trends indicate a significant shift in the epidemiology of HCC from viral-related to non-viral-related etiologies. Metabolic-associated fatty liver disease has emerged as the fastest-growing contributor to HCC in recent years, due to the increased prevalence of obesity and metabolic risk factors.[1,2] Metabolic-associated steatohepatitis (MASH) has also replaced chronic hepatitis as the leading cause of HCC among liver transplant candidates and recipients in the United States.[3] However, comprehensive demographic-specific data on the incidence and mortality of HCC remain limited.

Abboud and colleagues published an informative cross-sectional nationwide population-based time-trend analysis in *J Clin Transl Hepatol 2024*.[4] This study assessed the incidence and age-adjusted mortality rates of HCC in the United States from 2001 to 2020, using data from United States Cancer Statistics and National Center for Health Statistics of Centers for Disease Control and Prevention. Their nationwide study covered approximately 98% of patients diagnosed with HCC in the United States, revealing a nationwide increase in the incidence and mortality of HCC over the two-decade period in both men and women. Interestingly, among younger adults, there was a decreasing HCC incidence in men but not in women. This trend was observed across various racial/ethnic groups and was primarily attributed to tumors being diagnosed at an early stage. In terms of mortality, the analysis of the National Center for Health Statistics encompassed almost 100% of deaths attributed to HCC in the United States, showing a rise in HCC mortality rates in both sexes over the past two decades. Notably, while mortality rates in younger adults improved, the mortality rates in men improved at a greater rate compared to women, especially among the non-Hispanic American Indian/Alaska Native population.

The lower production of estradiol and a reduced response to estradiol contribute to greater progression of hepatic fibrosis and HCC in men and postmenopausal women, compared to premenopausal women.[5] Moreover, the decrease in hepatitis B and C contributions to HCC due to vaccinations and effective treatments, along with the non-decreasing trend of HCC in younger women and lesser relative improvement in mortality compared to men, is particularly concerning.

The authors postulate that this may be related to a disproportionate increase in the burden of non-alcoholic fatty liver disease, metabolic risk factors, and alcohol consumption in women.[6,7] This is supported by previous studies showing MASH as the fastest-growing etiology for HCC in both men and women, with mortality from MASH-related HCC in females approaching that of males, unlike other liver disease etiologies where male mortality far exceeds female mortality. Notably, the study also showed that age-standardized death rates from cirrhosis in females decreased across all etiologies over the study period, except in MASH, where age-standardized death rates remained stable.[8] The findings may also be attributed to a narrowing of sex differences in alcohol use, with data indicating increased alcohol consumption in women but not in men. Additionally, females appear more susceptible than males to alcohol-induced liver inflammation, leading to a more rapid progression to fibrosis.[9]

This study has several limitations. First, as a single-nation study, there is potential for selection bias, and the findings may not represent epidemiological data from other regions. Second, as the authors noted, the database may be subject to coding reliability issues and record losses, along with limitations due to the lack of variable data to assist in identifying risk factors associated with HCC incidence and mortality in different demographic-specific populations. Future analyses of male/female HCC survival rates in various racial/ethnic cohorts, beyond age-adjusted mortality rates, could provide insights into outcome disparities and inform targeted interventions.

Nonetheless, this large and comprehensive study adds to the growing body of literature on the epidemiology of HCC. Young females are more inclined to undergo and adhere to regular HCC surveillance.[10] However, given the findings of a non-decreasing trend of HCC in young females in this study, further large-scale prospective studies with longitudinal follow-up of female individuals with liver disease are warranted. These findings have important implications for clinical practice and healthcare policy, particularly in the increased detection of early-stage tumors, the implementation

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of lifestyle modifications, and targeted surveillance to reduce the burden of HCC.

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Conflict of interest

Daniel Q. Huang serves on the advisory board of Roche and Gilead. The other authors have no conflict of interests related to this publication.

Author contributions

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