



Changing patterns of etiology and management of hepatocellular carcinoma: need for global reappraisal

Teh-Ia Huo^{1,2,3}  · Shu-Yein Ho^{3,4} · Po-Hong Liu^{3,5}

Received: 3 February 2021 / Accepted: 6 February 2021 / Published online: 11 March 2021
© Japanese Society of Gastroenterology 2021

Keywords Hepatocellular carcinoma · Etiology · Management

To the Editor:

We read with interest the paper “The transition in the etiologies of hepatocellular carcinoma-complicated liver cirrhosis in a nationwide survey of Japan” by Enomoto et al. published in an upcoming issue of Journal of Gastroenterology [1]. It is an interesting study that looked at the changing etiology of hepatocellular carcinoma (HCC) between 1991 and 2010 in Japan. We have systematically investigated the changing clinical patterns of HCC in Taiwan [2], and found that Taiwan and Japan do share some similarities. In addition, a recent report from Italy somehow disclosed consistent findings which may deserve further discussion [3].

Taiwan is an endemic area for hepatitis B virus (HBV) infection and HCC. In a prospective cohort of 3349 HCC patients [2], we found several major timeline changes

between the period of 2004–2015. HCC patients with hepatitis B or C gradually but significantly decreased from 2004–2007 to 2012–2015. Notably, the proportion of patients diagnosed at early cancer stage increased from 33% in 2004–2007 to 37% in 2012–2015; this directly resulted in an increased probability of patients receiving curative treatment from 44% in 2004–2007 to 55% in 2012–2015 and improved patient survival. Alternatively, very similar changes are observed between Taiwan and Italy [3], including (1) increase of non-viral causes of HCC, (2) favorable cancer stage migration, (3) improved outcome of curative and non-curative treatments, and (4) improved overall survival in the last calendar period. Some of these features can be attributed to early detection of HCC through the surveillance program in high-risk subjects. A more apparent change is the evolution of the etiology of HCC from viral to non-viral causes. This is more likely due to the use of effective anti-viral therapy towards hepatitis B and C over the last decade that led to the rise of metabolic or alcoholic liver disease as a major etiology of HCC.

Chronic HBV infection is the leading cause of liver cirrhosis and HCC in most countries, except Japan, of Asia. We showed a remarkable decline in the incidence of HBV-associated HCC in the 12-year study period [2]. Several cohort studies suggested that the incidence of HBV infection significantly decreased after the initiation of hepatitis B mass vaccination program [4, 5]. In contrast, in Japan, hepatitis C virus (HCV) infection (60.3%) and HBV infection (12.9%) were the leading causes of HCC [1]. Given so, the rate of viral hepatitis-related HCC decreased from 85.3 to 64.4% due to specific anti-viral therapy for HCV and HBV. However, the changes of cancer stages and corresponding treatment modalities were not reported in

✉ Teh-Ia Huo
tihu@vghtpe.gov.tw

- ¹ Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan
- ² Institute of Pharmacology, National Yang Ming Chiao Tung University, Taipei, Taiwan
- ³ School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan
- ⁴ Division of Gastroenterology and Hepatology, Min-Sheng General Hospital, Taoyuan, Taiwan
- ⁵ Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

the current study and remain to be seen [1]. In our observation, patients with early cancer stage remarkably increased during the past 2 decades that resulted in a higher proportion of patients undergoing curative treatment and contributed to enhanced long-term survival. In summary, to reveal the mechanism of changing epidemiology, the timeline differences for HCC in its incidence, etiology, cancer stage, and therapeutic strategy requires more studies around the globe to clarify.

Authors' contributions Guarantor of the article: TIH. Specific author contributions: THH and PHL performed the research. SYH and TIH designed the study and wrote the paper. All authors approved the final version of the manuscript.

Financial support This study was supported by a Grant (VN110-06) from Taipei Veterans General Hospital, Taiwan.

Compliance with ethical standards

Conflict of interest statement There is no conflict of interest.

References

1. Enomoto H, Ueno Y, Hiasa Y, et al. The transition in the etiologies of hepatocellular carcinoma-complicated liver cirrhosis in a nationwide survey of Japan. *J Gastroenterol*. 2020. <https://doi.org/10.1007/s00535-020-01748-x> (**Online ahead of print**).
2. Ho SY, Liu PH, Hsu CY, et al. Evolution of etiology, presentation, management and prognostic tool in hepatocellular carcinoma. *Sci Rep*. 2020;10:3925.
3. Garuti F, Neri A, Avanzato F, et al. The changing scenario of hepatocellular carcinoma in Italy: an update. *Liver Int*. 2020. <https://doi.org/10.1111/liv.14735> (**Online ahead of print**).
4. Chang MH, Chen CJ, Lai MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med*. 1997;336:1855–9.
5. Chiang CJ, Yang YW, You SL, et al. Thirty-year outcomes of the national hepatitis B immunization program in Taiwan. *JAMA*. 2013;310:974–6.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.