Editorial Commentary

Surveillance for hepatocellular carcinoma in non-alcoholic fatty liver disease patients: towards personalized risk stratification

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Comment on: Cholankeril G, Kramer JR, Chu J, *et al.* Longitudinal changes in fibrosis markers are associated with risk of cirrhosis and hepatocellular carcinoma in non-alcoholic fatty liver disease. J Hepatol 2023;78:493-500.

Keywords: Surveillance; non-alcoholic fatty liver disease (NAFLD); risk stratification; longitudinal follow-up

Submitted Sep 24, 2023. Accepted for publication Oct 22, 2023. Published online Nov 08, 2023.
doi: 10.21037/hbsn-23-501
View this article at: https://dx.doi.org/10.21037/hbsn-23-501

Non-alcoholic fatty liver disease (NAFLD), now referred to as metabolic-associated steatotic liver disease (MASLD), is a highly prevalent disease affecting 32% of the global population (1). Notably, NAFLD can progress to steatohepatitis, liver cirrhosis (LC), and hepatocellular carcinoma (HCC). Early diagnosis of HCC through appropriate surveillance of high-risk patients is essential.

Despite being a leading cause of pre-cirrhotic HCC (2), there is no consensus regarding the need for HCC surveillance in non-cirrhotic NAFLD patients. Currently, the American Association for the Study of Liver Diseases (AASLD) guideline recommends biannual HCC surveillance in patients with LC, but not in patients with NAFLD without cirrhosis (3). The American Gastroenterological Association (AGA) also recommends HCC surveillance in patients with LC, but mentions that NAFLD patients with advanced fibrosis may be offered HCC surveillance (4).

HCC surveillance is cost-effective in groups with an annual risk of HCC of 1.5%; however, the AASLD recently proposed a lower threshold of 0.8% (3). Regardless of etiology, in LC patients, the annual risk of HCC is 0.8% or more, which makes their biannual HCC surveillance reasonable (3). However, NAFLD patients with advanced fibrosis without cirrhosis exhibit an annual risk below this threshold. Several guidelines recommend considering HCC surveillance in NAFLD patients with advanced fibrosis, emphasizing the significance of identifying high-risk HCC patients in this population (4,5). This could be attributed to the high proportion of HCC cases among pre-cirrhotic NAFLD patients. In other etiologies, most of the HCC patients have underlying LC, accounting for about 86% of HCC patients (6). However, 20–50% of NAFLD-related HCC cases are pre-cirrhotic patients (2). Furthermore, the incidence of NAFLD-related HCC is increasing. Therefore, further stratification of pre-cirrhotic NAFLD patients based on their HCC risk is essential for surveillance guidelines.

Recently, Cholankeril *et al.* demonstrated a significant association between longitudinal changes in the fibrosis-4 (FIB-4) index in NAFLD patients and the risk of LC and HCC (7). The fibrosis stage is a significant predictor of LC and HCC risk although other factors, including past fibrosis indexes, can also contribute to this risk. For instance, LC patients with a persistently low FIB-4 index over the past 3 years have HCC incidence of 3.43 per 1,000 person-years, which is comparable to that observed in patients with

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advanced fibrosis (incidence of 0.34 per 100 person-years) (8). Furthermore, patients with an indeterminate or high FIB-4 index, even with a low index over the past 3 years, exhibit an HCC incidence of 5.94 per 1,000 person-years, which is below the threshold for surveillance. Therefore, high-risk pre-LC patients are at risk of developing HCC comparable to low-risk LC patients, emphasizing the significance of individualized HCC risk assessment. Thus, it can be concluded that the high-risk subset of pre-cirrhotic patients has a comparable HCC risk to the low-risk proportion of LC patients, emphasizing the importance of individualized HCC risk assessment.

Currently, HCC surveillance for NAFLD patients is based primarily on the fibrosis stage (3-5). However, the fibrosis stage and cirrhosis are not the only predictors that can predict HCC risk. Genetic polymorphisms, such as variants in PNPLA3, TM6SF2, GCKR, MBOAT, and HSD17B13, are associated with HCC risk in NAFLD patients. Notably, a polygenic risk score has been developed, successfully predicting HCC risk in LC and non-LC patients; this score serves as a valuable tool for stratifying patients based on HCC risk (9). Significant risk factors, such as type 2 diabetes mellitus (T2DM), ethnicity, and old age, can also be considered in HCC risk stratification of NAFLD patients (6,10). Furthermore, ultrasonography and magnetic resonance image (MRI)-based tests are heavily focused on measuring fibrosis stage. Although current evidence indicates their association with liver-related outcomes, further research is needed to develop accurately HCC risk prediction models for NAFLD patients (11).

Among the risk factors for HCC development in NAFLD patients, T2DM is considered the most significant predictor of fibrosis progression and HCC development (12). Notably, T2DM affects approximately 10% of the worldwide population; moreover, the increasing prevalence of this condition suggests that a larger number of individuals may be affected in the future (13). Consequently, the number of individuals in high-risk groups for fibrosis progression and HCC is expected to increase, requiring additional screening measures within these populations.

Race is a crucial factor to consider in the development of an HCC risk prediction system. For instance, when FIB-4 was developed, 78% of the cohort was Caucasian. Therefore, the score may be more accurate for Caucasian patients. A report pointed out the lower predictive accuracy [area under the receiver operating characteristic curve (AUROC) of 0.58] for this score among Korean patients compared to the original AUROC of 0.765 (14). Particularly, Asian populations exhibits distinct characteristics relevant to NAFLD, such as a lower body mass index and a higher prevalence of T2DM, a major predictor for HCC development (10). Therefore, HCC surveillance in Asians is based on risk stratification using data specific to this population. More research is needed to validate the association between longitudinal changes in the FIB-4 index and the risk for LC and HCC.

The choice of screening method is another important factor to consider. Most guidelines, including those of the AASLD and AGA, recommend ultrasonography with or without measurement of the alpha-fetoprotein as the standard surveillance approach (4,12). However, the effectiveness of ultrasonography is highly dependent on the operator and suboptimal results may be obtained in obese patients (3). Moreover, a study suggests MRI-based surveillance has demonstrated superior efficacy in detecting very early-stage HCC compared to ultrasonography-based surveillance (15). Although considering MRI-based surveillance for high-risk patients is reasonable, its cost-effectiveness may vary by country. In this context, risk stratification remains pivotal for identifying patients who would benefit from MRI-based HCC surveillance.

Although the current screening systems are well-designed and cost-effective, further research is needed to improve personalized risk stratification and identify the most appropriate surveillance method. Additionally, current scoring systems and risk factors should undergo more comprehensive validation in Asian populations.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-501/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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Cite this article as: Kim K, Park JY. Surveillance for hepatocellular carcinoma in non-alcoholic fatty liver disease patients: towards personalized risk stratification. HepatoBiliary Surg Nutr 2023;12(6):927-929. doi: 10.21037/hbsn-23-501