Editorial

Hepatocellular carcinoma in non-alcoholic fatty liver disease from a clinical and public health perspective

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Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in the western world (1). Currently, the global prevalence of NAFLD is estimated at 30% and is notably higher in South America and the Middle East (1). NAFLD prevalence has been rising during the last decades, and cases of decompensated NAFLD cirrhosis could increase by 168% in 2030 (*Figure 1A*) (2). These trends are probably explained by several factors including the decrease in viral hepatitis incidence and the increasing prevalence of obesity and type 2 diabetes mellitus (T2DM) among the general population (2). In fact, NAFLD is extremely frequent in metabolic diseases, reaching 65% in patients with overweight, 90% in patients with obesity, and up to 70% in patients with T2DM (3). NAFLD encompasses a broad spectrum of clinical phenotypes, ranging from isolated steatosis, different degrees of inflammation and fibrosis, to cirrhosis and its complications (4). Cancer also constitutes a significant cause of death in NAFLD patients, mainly due to hepatocellular carcinoma (HCC) and other neoplasms, such as colorectal and breast cancer (5). HCC is the third leading cause of cancer-related deaths worldwide (6). NAFLD contributes to the development of HCC, and the rise in the NAFLD prevalence might trigger an excessive increase in HCC incidence during the following decades (*Figure 1B*) (2). Around 80% of HCC cases are developed in patients with cirrhosis; however, a recent systematic review evidenced that NAFLD-related HCC is associated with a higher proportion of patients without cirrhosis (6). Several risk factors have been related to the development of NAFLD-related HCC in those without cirrhosis, including older age, male patients, smoking history, T2DM, and elevated alanine aminotransferase levels (7). Although the pathogenesis of NAFLD-HCC is poorly understood, several factors have been proposed, including chronic inflammation, hyperinsulinemia, adaptive immune responses, hepatic progenitor cell populations, and genetic susceptibility (8). Of note, obesity has a nonlinear dose-dependent effect increasing risk for different cancer sites, including HCC (9). In addition, T2DM is associated with a greater than 2-fold increase in HCC risk, even after adjustment for anthropometric, demographic factors, comorbidities, and liver disease etiology (9). Multiple genetic polymorphisms have also been associated with an increased risk of NAFLD-related HCC, including variants of the patatin-like phospholipase domain-containing protein 3 (PNPLA3), transmembrane 6 superfamily member 2 (TM6SF2), and membrane-bound O-acyltransferase domain-containing 7 (MBOAT7) genes, which are highly prevalent in some ethnicities (9).

In this context, Geh *et al.* reviewed the challenges in clinical practice to screen, diagnose, and treat patients

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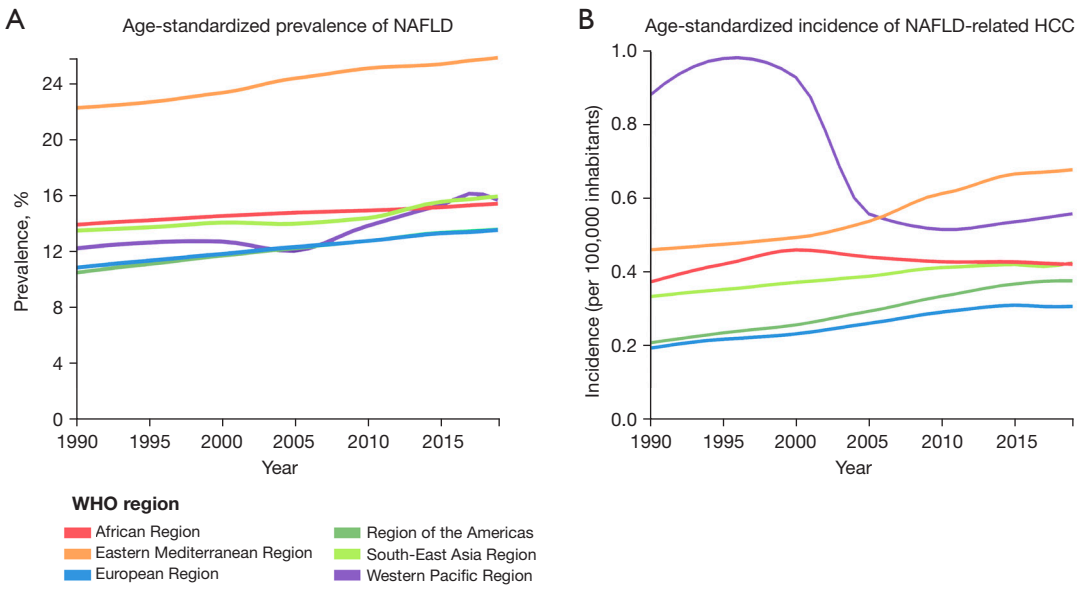

Figure 1 Trends in (A) prevalence of NAFLD and (B) incidence of NAFLD-related HCC according to WHO regions. Data were obtained from the Global Burden of Disease Collaborative Network. Seattle, United States of America: Institute for Health Metrics and Evaluation, 2022. NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma; WHO, World Health Organization.

with NAFLD-related HCC (8). The current guidelines recommend screening for HCC in all patients with cirrhosis or advanced fibrosis. However, detection of HCC seems to be suboptimal in NAFLD patients as tumors tend to be diagnosed at a more advanced stage than other related etiologies (8). Several factors contribute to this decreased performance, including underdiagnosis of advanced fibrosis in NAFLD, inadequate surveillance for HCC in NAFLD, and the limitations of several imaging methods in this population.

Detecting advanced fibrosis and cirrhosis in NAFLD patients is the cornerstone to delimiting populations at higher risk of HCC. However, most clinicians do not assess the presence of advanced fibrosis and cirrhosis in NAFLD and NAFLD-related comorbidities, even with a significant prevalence of advanced fibrosis such as that seen in diabetic patients, which reaches up to 13% (3). In addition, a significant proportion of patients with cirrhosis due to NAFLD have normal or slightly abnormal liver tests, which does not contribute to raising awareness and clinical suspicion. Multiple non-invasive tests are available to exclude low-risk individuals, reaching a high negative predictive value excluding advanced fibrosis in NAFLD patients (10). Fibrosis-4 (FIB-4) and the NAFLD Fibrosis Score (NFS) are among the most widely validated and recommended by clinical guidelines, with a sensitivity and specificity of 43–44% and 81–90% for advanced fibrosis, respectively (10). These tests have a low cost and high accessibility in routine clinical practice. Nevertheless, due to their low sensitivity, several patients could require an additional non-invasive test or liver biopsy (especially in case of diagnostic uncertainty). Notably, a recent study including 2,566 patients with NAFLD demonstrated that polygenic risk scores could improve the accuracy of NAFLD-related HCC detection and stratification of HCC risk, even in the absence of advanced fibrosis (11). However, it is unclear which is the best non-invasive test to stratify the HCC risk in individuals with NAFLD in clinical practice.

There are lower HCC surveillance rates in NAFLD patients than in other liver diseases. Although a poor detection of individuals with advanced fibrosis is critical, other factors contribute, including the low availability of local clinical guidelines in NAFLD and the lack of referral algorithms for patients at higher risk (12). For example, a recent study showed that only 35% of American countries had published national clinical NAFLD guidelines, and only 29% had referral algorithms for diagnosing and managing patients with NAFLD (12). In addition, lack of regular outpatient care, a lack of screening orders in those with known cirrhosis, and adherence to screening ultrasound appointments (13). Furthermore, ultrasound has important limitations in identifying small lesions in individuals with

severe steatosis or obesity. Consequently, novel surveillance strategies for HCC should be developed to overcome these limitations in patients with NAFLD (8).

Most classification systems and therapeutic recommendations are endorsed for cirrhotic patients. As mentioned above, a significant fraction of patients with NAFLD-related HCC does not have cirrhosis. Thus, this group of patients does not have complications due to portal hypertension while they might face the presence of relevant comorbidities, including obesity, T2DM, hypertension, dyslipidemia, and cardiovascular disease (8). Several comorbidities have been associated with a higher risk of post-resection liver failure, postoperative wound infections, and short-term mortality after liver transplantation (8). Proper management of cardiovascular disease and comorbidities should be encouraged in all patients with NAFLD-related HCC (4). A good selection of individuals undergoing liver resection is crucial to avoid postoperative complications and mortality (8). Loco-regional and systemic therapies might also have a lower response in the presence of NAFLD or comorbidities, and multiple variables should be considered in the decision-making. Further studies are required, especially including patients with comorbidities and older age, which usually have a higher risk of HCC while they are often excluded from randomized clinical trials.

Governmental agencies should establish policies and countermeasures to decrease the enormous disease burden due to NAFLD. Unfortunately, recent evidence showed that no American country has a national policy or action plan addressing NAFLD (12). This finding was similar to a study assessing 102 countries worldwide (14). Regrettably, 31% had no preparedness to address NAFLD at a national level, only 31% had national NAFLD clinical guidelines, and NAFLD was rarely considered in the strategies of related conditions (14). It is vital to promote disease awareness, increase educational opportunities for healthcare personnel and the general public, repair health system fragmentation, and establish effective strategies for preventing and treating NAFLD and common comorbidities. The cross-sector collaboration between scientific societies, governments, non-governmental organizations, the pharmaceutical industry, and other stakeholders is essential to incorporate the NAFLD in the public health policies agenda and address the rise in NAFLD-related HCC (15).

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Footnote

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