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Changing etiology and epidemiology of hepatocellular carcinoma: Asia and worldwide

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Approximately 80% of hepatocellular carcinoma (HCC) cases arise in sub-Saharan Africa and Eastern Asia, following a similarly high prevalence of chronic hepatitis B virus (HBV) carriers in these regions. The etiology and epidemiology of HCC have recently changed worldwide. Although HBV infection is the main contributor to HCC development, a slow but continuous decline in HBV infection rates has been reported since 1990. Owing to the widespread use of direct-acting antivirals, the incidence of hepatitis C virus-related HCC has remarkably decreased in Japan and European countries. In Korea, Taiwan, and Singapore, the incidence of HBV-related HCC has significantly decreased owing to vaccination against HBV. Globally, while HBV accounted for more than half of HCCs in 1990, this had decreased to 42% in 2019. In contrast, the proportion of patients with alcoholic- and nonalcoholic steatohepatitis (NASH) increased from 13% to 18% and from 5% to 6%, respectively. NASH-related HCC has characteristics that differ from those of virus-associated HCC. Compared with other etiologies, patients with NASH-associated HCC are older, have a higher body mass index, and have higher rates of type 2 diabetes mellitus, hypertension, hyperlipidemia, and cardiovascular disease. Nonalcoholic fatty liver disease (NAFLD)-associated HCC is also known to develop in the absence of cirrhosis, unlike alcohol-related and autoimmune liver diseases. Because patients with NAFLD usually have diabetes or obesity, surveying this population is challenging. Optimal selection of the target population and surveillance tools among patients with NAFLD needs to be determined. **(J Liver Cancer 2024;24:62-70)**

Keywords: Carcinoma, hepatocellular; Epidemiology; Non-alcoholic fatty liver disease

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for 80-90% of all cases.[1] This malignancy causes a serious health and economic burden globally, especially in Asia.[2] It is the third leading cause of cancer-related death globally, with a 5-year survival rate of approximately 18%.[3] After lung cancer, liver cancer (HCC and cholangiocarcinoma) ranked as the second most significant contributor to years of life lost due to cancer globally from 2005 to 2015, with a 4.6% increase in absolute years of life lost.[4,5] Approximately 80% of HCC cases arise in sub-Saharan Africa and Eastern Asia, aligning with the high

prevalence of chronic hepatitis B virus (HBV) carriers in these regions. HCC is the second leading cause of malignant deaths in Asia. The recent shift in overall trends in HCC incidence over time is explained by the worldwide vaccination program against HBV, active antiviral treatment using nucleoside/nucleotide analogs, introduction of direct-acting antiviral agents (DAA) for chronic hepatitis C, global efforts to eliminate viral hepatitis, and increasing rates of alcohol use and obesity, which influence the prevalence of alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD). The overall global burden of HCC has increased over time.

GEOGRAPHIC VARIATION OF HCC INCIDENCE AND MORTALITY

Significant differences exist worldwide in the incidence and mortality of HCC, primary due to differences in the timing and exposure to environmental and infectious risk factors, accessibility to healthcare resources, and the capability to detect early-stage HCC and provide potentially curative treatment.[6] High incidence and mortality rates of 22-24 per 100,000 were reported for Thailand, Vietnam, and Cambodia in 2020, while Mongolia had the highest incidence and mortality rates worldwide at >80 per 100,000 persons. China had the highest number of individuals affected by HCC, followed by Japan, Thailand, and Vietnam (Table 1).[7] The GLOBOCAN 2020 data demonstrates a trend that many countries with previously low HCC incidence, including Iran, Afghanistan, Qatar, Azerbaijan, Iraq and Nepal, have experienced a tremendous increase in the past 2 years.[8] In the United States, the incidence of HCC has tripled over the last four decades, possibly due to the maturity of the patient pool with chronic hepatitis C. The burden of HCC is expected to reach 22 million cases in the next 2 decades in this country.[9] The incidence in Japan has dropped drastically with a significant reduction in the population infected by hepatitis C virus (HCV). Similarly, HCC incidence in China is declining owing to increasing vaccination against hepatitis B.[10] In Korea, the age-standardized incidence of liver cancer significantly decreased from 28.9 in 1999 to 19.7 in 2014 and 16.1 in 2019.[11] The age-standardized death rate from liver cancer notably declined from 24.7 in 1999 to 16.4 in 2014

and further to 11.5 in 2020. However, the annual crude incidence rate of liver cancer has risen over the last 2 decades, from 28.1 in 1999 to its peak at 32.8 in 2010 and 31-32 in 2015. Additionally, the yearly absolute number of deaths has also increased over the same period, rising by 19.4% from 9,682 in 1999 to 11,566 in 2014, and then decreasing by 8.6% to 10,565 in 2020.[11] Such a discrepancy between crude mortality rate and age-standardized mortality rate might be due to anti-HBV vaccination, widespread use of antiviral agents and the aging population.[12] In 2019, the Western Pacific region demonstrated the highest frequency of incident liver cancer cases (n=295,484), deaths (n=254,054), and disability-adjusted life-years (DALYs; 6.7 million). However, interestingly, the US had the greatest increase between 2010 and 2019 in liver cancer incident cases (+41%), deaths (+42%), and DALYs (+36%).[13] Lastly, despite a slowly decreasing trend in global age-standardized incidence rates of HCC since the late 1990s, the total number of HCC cases has been increasing owing to aging and population growth. In 2019, approximately 747,000 cases of HCC were reported worldwide, a 70% increase from 1990. While the global age-standardized incidence rates have been decreasing slowly since 2000, the rates have been increasing in countries with high sociodemographic indices since 1990. For example, the incidence of HCC in the United States has increased 2-3 fold over the past 3 decades owing to the high prevalence of HCV infection and NAFLD.[6]

Table 1. Incidence and mortality of HCC by country[7]

Country	Incidence		Mortality	
	Case	ASR (%)	Case	ASR (%)
China	410,038	18.2	391,152	17.2
Japan	45,663	10.4	28,155	4.8
Thailand	27,394	22.6	26,704	21.9
Vietnam	26,418	23.0	25,272	21.9
Indonesia	21,392	7.9	20,920	7.7
Republic of Korea	14,788	14.3	11,158	9.9
Philipphines	10,594	11.4	9,953	10.8
North Korea	5,607	15.5	5,228	14.4
Myanmar	5,466	10.0	5,281	9.7
Cambodia	3,142	24.3	2,946	22.9
Mongolia	2,236	85.6	2,060	80.6
Lao	1,272	24.4	1,192	22.9
United States	42,284	6.9	31,078	4.7

Incidence and mortality of HCC data adapted by GLOBOCAN 2020.
ASR, age-standardized rate per 100,000; HCC, hepatocellular carcinoma.

CHANGING ETIOLOGY OF HCC IN ASIA AND WORLDWIDE

Chronic HBV infection is a major global health problem with high prevalence, that can lead to cirrhosis as well as HCC.[14,15] HBV is endemic in East and South-East Asia with the exception of Japan.[16] Globally, an estimated 71 million individuals were infected with HCV in 2015.[17] The annual risk of developing HCC with chronic hepatitis C ranges from 1.2% to 1.7%, and for individuals with cirrhosis, it varies from 1.4% to 2.5%.[18] Although HBV is the primary cause of HCC, there has been a gradual but steady decrease in HBV infection rates in both global and Asia populations since

1999, according to the Global Burden of Diseases.[19] Currently, the highest incidence and prevalence rates of HCC are observed in East Asia, North Africa, and Southeast Asia, regions where there is a higher prevalence of chronic HBV infection, contributing to over half of the global HCC cases. Conversely, cases associated with HCV, the main risk factor in the Mediterranean region, the United States, and Pakistan, have notably decreased due to the use of DAAs.[20-22] Notably, in Taiwan, the mortality rate from HCC significantly dropped among individuals aged 5 to 29 years, from 0.81 deaths per 100,000 to 0.05 per 100,000, during 2001-2004, among those born in 1977-1980, attributed to the immunization campaign in 1984.[23] Similarly, Hong Kong has witnessed a
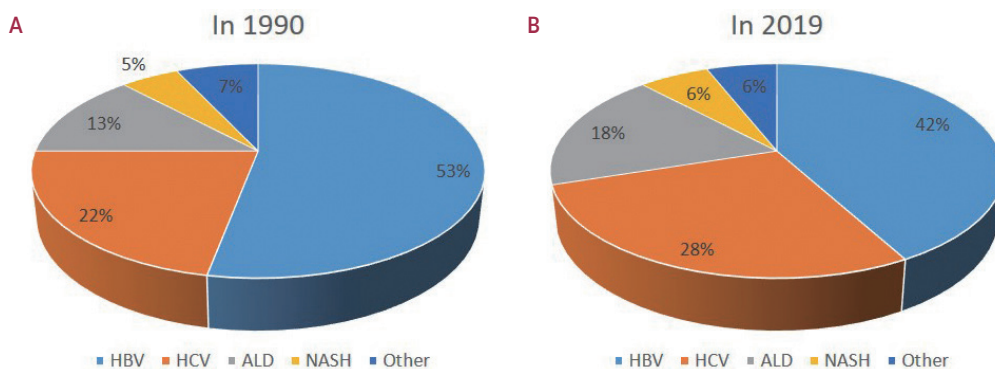

Figure 1. Proportion of HCC etiologies in the world showing a transition from viral hepatitis to nonviral etiologies between 1990 (A) and 2019 (B). Modified from Yang et al.[25] and Toh et al.[26] with permission. HBV, hepatitis B virus; HCV, hepatitis C virus; ALD, alcoholic liver disease; NASH, nonalcoholic steatohepatitis.
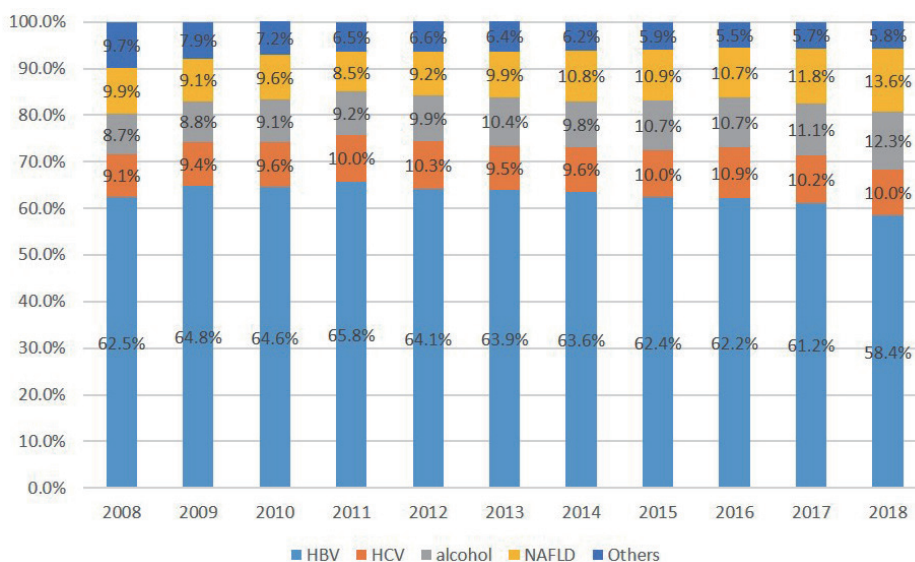

Figure 2. Distribution of HCC etiologies demonstrating increase of NAFLD between 2008 and 2018 in South Korea. Adapted from the Korean Association for the Study of the Liver[27] with permission. HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; HCC, hepatocellular carcinoma.

significant decline in HCC incidence across all age groups over the past 25 years, partly due to a decline in HBV infection rates since the introduction of universal HBV vaccination in 1988.[24] According to the Global Burden of Disease study,[25] there are temporal and geographical differences in HCC etiologies. Clearly, there was a transition from chronic viral hepatitis to a non-viral etiology between 1990 and 2019. Although HBV accounted for more than half of all cases in 1990, the proportion decreased to 42% in 2019. In contrast, the proportion of patients with alcoholic and non-alcoholic steatohepatitis (NASH) increased from 13% to 18% and from 5% to 6%, respectively. Regarding the distribution of HCC etiologies in various world regions in 2019, chronic viral hepatitis was still the main cause of HCC in Asia and most African regions, whereas non-viral causes such as NASH and ALD contributed to the majority of HCC cases in North America, Europe, and Australia (Fig. 1).[25,26] In Korea, the hepatitis B surface antigen (HBsAg) positivity rates were high, exceeding 8% in the 1980s. However, with the introduction of HBV vaccination in 1983 and the implementation of the national immunization program in 1985, HBsAg-positive rates have decreased. These rates have further decreased since 2002, owing to the implementation of a perinatal infection prevention program. Fig. 2 shows the change in the proportion of HCV as an etiology of HCC between 2008 and 2018. The incidence of HBV-related HCC decreased, while the incidence of alcohol- and NAFLD-associated HCC increased from 8.7% and 9.9% to 12.3% and 13.6%, respectively (Fig. 2).[27] Of note, HBV is still the most common etiology in Asia. In 1990, HBV infection caused more than half of all HCC cases worldwide. In 2019, this figure had decreased to 41%. Nonetheless, it remains the most common cause of HCC worldwide. In the Asia-Pacific region, HBV infection is the major cause of HCC, accounting for more than 60% of all HCC cases. In Korea, 70-80% of patients with HCC have current or past HBV infection.

GLOBAL BURDEN OF ALCOHOL-ASSOCIATED HCC

ALD is one of the most prevalent liver diseases in the United States and Europe.[28] Chronic, excessive alcohol intake, defined as consuming >40 g of pure alcohol per day (equivalent to 375 mL of 13 vol% wine or >1 L of 5 vol% beer) over an extend period, poses the greatest risk of ALD.[29] However, a recent meta-analysis has demonstrated even consuming 12-24 g of alcohol per day chronically increases the risk of cirrhosis compared to abstaining from alcohol.[29] When all World Health Organization regions are considered, adult per capita alcohol consumption has risen by approximately 10% over the past 25 years,

mostly owing to significant increases in Asia (particularly in China and India) and Africa, whereas in North and South America and in Europe consumption decreased by 1% and 10%, repectively.[30] In 2019, an estimated 19% of all liver cancer deaths worldwide were attributed to alcohol, lower than those caused by HBV infection (40%) and HCV infection (29%).[13] Regional differences were observed in the percentage of liver cancer deaths related to alcohol, with Europe having the highest percentage (35%) and the Eastern Mediterranean region the lowest (10%).[13] Alcohol was the second-fastest rising contributor to the global liver cancer age-standardized death rate, with the Americas experiencing the highest increase. Global alcohol per capita consumption is projected to continue rising, especially in the Western Pacific and Southeast Asia, due to economic growth in densely populated regions.[31] Therefore, more effective strategies must be put in place to reduce alcohol consumption.

EPIDEMIOLOGICAL CHARACTERISTICS OF NAFLD-ASSOCIATED HCC

NAFLD is the most common liver disease in the world. Its global prevalence in 2016 was approximately 25%, ranging from 13% in Africa to 42% in Southeast Asia, with a projected 15-56% rise by 2030.[32,33] In particular, the prevalence of NASH is projected to increase by up to 56% between 2016 and 2030 in China, France, Germany, Italy, Spain, Japan, the UK and the United States.[33] While NAFLD, being related to the metabolic syndrome, has been considered prevalent primary in the Western world, recent years have seen its rise in Asia, paralleling lifestyle changes amid rapid economic growth. Studies reveal a rise in NAFLD prevalence in Asian countries from 25.3% (1999-2005) to 33.9% (2012-2017), underscoring this trend.[34] Compared with other etiologies, patients with NASH-associated HCC are older (mean difference, 5.6 years); have higher body mass index (mean difference, 3 kg/m^2); and have higher rates of type 2 diabetes mellitus (DM) (odds ratio [OR], 4.3), hypertension (OR, 2.8), hyperlipidemia (OR, 3.4), and cardiovascular disease (OR, 2.2).[35] NAFLD-associated HCC is also well known to develop in the absence of cirrhosis, unlike liver diseases of other etiologies such as alcohol-related and autoimmune liver disease.[36,37] In a Korean study, the clinical and survival outcomes of NAFLD-HCC and HBV-HCC were compared. The 232 patients underwent surgical resection; 32 had NAFLD-HCC and 200 had HBV-HCC. Before propensity score match (PSM), cirrhosis was more frequently detected in patients with HBV-HCC (55% vs. 15%, P<0.001) and the average tumor size was larger in the NAFLD-HCC group than in the HBV-HCC group (4.4±3.3 cm vs. 3.4±1.8 cm, P=0.014). After PSM, the 5-year overall survival

rates were similar (60% vs. 63%, P=0.978) between the two groups.[38] NAFLD has now become the fastest-growing cause of HCC among liver transplant recipients and candidates on the waiting list in the United States,[39] with similar trends observed in Europe, South Korea, and Southeast Asia over the past 2 decades.[40,41]

HCC INCIDENCE AMONG PATIENTS WITH NAFLD IN DIFFERENT REGIONS

The incidence of HCC among patients with NAFLD differs substantially according to the stage of hepatic fibrosis and the presence of accompanying metabolic diseases such as obesity or DM. In the United States and Europe, the annual HCC incidence in cohorts of patients with NASH ranges from 0.7% to 2.6%.[42,43] It was found, in a United States study, that 10 of 149 patients with NAFLD who had biopsy-proven cirrhosis developed HCC over 10 years.[43] The HCC incidence in patients with cirrhosis due to NASH was higher in older patients, in males, and in patients with DM and higher alcohol consumption.[44] The annual incidence of HCC was found to be 0.5% in a cohort of 41 patients with cirrhosis and NASH in a prospectively conducted study in India.[45] Emerging evidence suggests that HCC can develop in NASH patients without cirrhosis; for instance an Italian study of 145 patients with NAFLD-associated HCC found that half of them lacked cirrhosis.[46] It is noteworthy that patients without cirrhosis mainly had NASH with advanced fibrosis rather than simple fatty liver without fibrosis, emphasizing that the stage of fibrosis might be meaningful in hepatocarcinogenesis in the absence of cirrhosis.[47] The incidence of HCC in patients without cirrhosis with NAFLD or NASH ranges from 0.1 to 1.3 per 1,000 patient-years.[48] Though the HCC incidence among patients with NAFLD is significantly lower in those without cirrhosis than in those with cirrhosis, the HCC prevalence among patients with noncirrhotic NAFLD is high owing to the high frequency of patients who have NAFLD with fibrosis of any stage. A Japanese study reported an annual HCC incidence of 0.043%, based on a cohort of 6,508 patients with NAFLD diagnosed using ultrasonography. The cohort consisted largely of patients without cirrhosis or simple fatty liver because the aspartate aminotransferase to platelet ratio index was >1.5, in only 2.8% of patients.[49] A Korean study of 8,721 patients with NAFLD diagnosed using ultrasonography demonstrated an HCC incidence of 23 per 100,000 patient-years. In the study, 25% of patients had an intermediate or high NAFLD fibrosis score.[50] In a study of a Taiwanese cohort, the authors found a 10-year HCC incidence of 2.73%, which was similar to that observed in the Korean study.[51]

PROPORTION OF NAFLD AS AN ETIOLOGY OF HCC IN DIFFERENT REGIONS

Globally, the estimated proportion of patients with HCC with NAFLD ranges from 1% to 38% in different countries/regions. In a study using a Markov model, it was suggested that the incidence of NAFLD-associated HCC in England would increase by 88% between 2016 and 2030, from 850 to 1,600 cases.[33] Among European countries, Germany is projected to have the highest prevalence of NAFLD-associated HCC (4,090 cases) in 2030 because of its high projected incidence of NASH (4.7 million by 2030).[33] The prevalence of cryptogenic HCC in Southeast Asia ranges from 12.6% in Singapore to 24.9% in the Philippines.[52] In the United States, a moderate proportion of HCC is ascribed to NAFLD. In Brazil, the prevalence of NAFLD-related HCC is rapidly increasing. Among patients with HCC who require liver transplantation, those with NASH comprise the second largest group after those with HCV infection. The prevalence of NASH-associated HCC increased from 8.3% in 2002 to 13.5% in 2012 in a study using the United Network for Organ Sharing registry.[53] The prevalence of NAFLD-related HCC increased from 2.6% (1995-1999) to 19.5% (2010-2014) in a French study with 323 patients with HCC who received liver resection at two centers between 1995 and 2014.[54] In the most of patients with HCC in China, HBV is still the dominant etiology. Only 1% of 8,683 Chinese patients with HCC were ascribed to NAFLD in a study with patients who were diagnosed between 2005 and 2011.[55] However, with increasing numbers of patients with NAFLD, estimated to be 243.7 million currently, and in the near future due to ageing population, the prevalence of NAFLD-related HCC is projected to rise from 14,090 cases in 2016 to 26,240 cases by 2030.[33,56]

NAFLD AS AN EMERGING HCC ETIOLOGY IN ASIA

Previously, NAFLD was predominantly considered a liver disease affecting Western populations. However, since 1990, the prevalence of NAFLD in Asia has risen significantly. In 2019, the Asian population accounted for 48.3% of global NAFLD-associated liver complications such as cirrhosis and HCC, surpassing even European and United States population.[57] In China, both NASH and ALD contributed to approximately 13% of HCC cases in 2019,[31] possibly driven by factors such as the rapid economic growth, increased alcohol consumption (from 4 L per capita in 2005 to 7 L in 2016), sedentary lifestyles, and escalating rates of obesity and DM (increasing by 2-3% between 2014 and 2018).[58] By 2020, NASH

and ALD affected 2-6% and 1-8% of the general population, respectively, with a projected 48% increase in NASH prevalence by 2030.[59] In Japan, HCC prevalence has surged over the years, due to the increase in NASH and ALD.[31] In particular, between 1996 and 2019, the prevalence of non-viral HCC escalated from 12% to 46%, mirroring the rise in obesity, metabolic syndrome, and alcoholism in this country.[60] The prevalence rate of NAFLD in Japan nearly doubled from 13% (in the early 1990s) to 25-35% (in the early 2000s), and is predicted to affect 45% of the population by 2040.[61] In Korea, a study revealed a rise in the proportion of HCC associated with NAFLD from 3.8% in 2001-2005 to 12.2% in 2006-2010.[40] While data from other countries are lacking, the incidence of NAFLD-associated HCC is expected to surge in the future, given the development of NAFLD in many Asian countries over the past 2 decades due to sedentary lifestyles and over-nutrition.[62]

HOW TO COPE WITH INCREASING PATIENTS WITH NAFLD-HCC

To increase the number of patients with NAFLD globally, physicians need to control NAFLD epidemiology, screen for NAFLD among patients with metabolic diseases, identify surveillance methods and targets for patients with NAFLD, and optimize treatment for patients with NAFLD-associated HCC. The description of measures to prevent NAFLD in the general population is beyond the scope of this study. Type 2 DM is one of the strongest risk factors for the development of NASH, advanced fibrosis/cirrhosis, HCC, and mortality.[63,64] It is estimated that 40-70% of patients with type 2 DM have underlying NAFLD, and among those, 37% have NASH and 17% will develop advanced fibrosis.[65] NASH, and most importantly, the presence of advanced liver fibrosis, are key determinants of long-term prognosis and are associated with a high rate of liver-related mortality.[66] Therefore, identifying patients at high risk earlier in the disease course is critical to prevent and monitor the risk of liver-related complications, such as liver failure and HCC. Although NAFLD is a prevalent disease in the general population, only a minority of patients with NAFLD develop NASH and advanced liver fibrosis, placing them at a higher risk of developing liver-related complications. This group of patients should be evaluated and managed by specialists to prevent and monitor liver-related complications. A recent publication by the United States members of the Global NASH Council recommended stratifying patients based on metabolic risk factors, including type 2 DM, utilizing fibrosis-4 (FIB-4) as the initial assessment tool. In a patients with DM, stratification would be by identifying one

additional metabolic syndrome feature (weight circumference >40 inches in men, 35 inches in women; triglycerides ≥150 mg/dL; high density lipoproten-cholesterol <40 mg/dL in men, 50 mg/dL in women; systolic blood pressure ≥130 mmHg and/or diastolic pressure ≥85 mmHg). For those without DM, at-risk patients are identified by having three metabolic risk factors (including elevated fasting glucose ≥100 mg/dL). Patients with a FIB-4 score ≥1.3 should undergo further evaluation by a liver specialist.[67] The use of a noninvasive scoring system, such as NAFLD fibrosis score as well as FIB-4, is the simplest and most accurate strategy to identify patients at high risk of advanced fibrosis.[68] In another recent article, the authors recommend the use of FIB-4 and/or vibration controlled transient elastography (VCTE) according to local resources, availability, and clinical context. The proposed algorithm involves a first-step annual FIB-4 score followed by VCTE for those with indeterminate or a high-risk score (FIB-4 ≥1.3). Patients at low risk (FIB-4 <1.3 or VCTE <8 kPa) can be followed up by primary care physicians for lifestyle changes and yearly calculation of FIB-4, while patients at high risk (FIB-4 ≥1.3 or VCTE ≥8 kPa) should be referred to liver-specialist clinics for further assessment and evaluation.[69] As the risk of liver fibrosis increases according to the number of metabolic risk factors such as hypertension and hyperlipidemia, it might be important to pay more attention to the patients with multiple metabolic risk factors and to proactively monitoring NASH progression in these patients. Because nearly one-fourth of NAFLD-related HCC cases occur in the absence of cirrhosis, it is difficult to include patients with noncirrhotic NAFLD in the surveillance program. However, these patients have a very low annual HCC incidence of 0.008 per 100 person-years, so surveillance is not cost-effective in this population.[70] The American Association for the Study of Liver Diseases guidelines recommend HCC surveillance for patients with cirrhotic NAFLD, but not for patients with noncirrhotic NAFLD.[71] On the other hand, the European Association for the Study of the Liver (EASL) highlights the importance of categorizing those who should be screened for HCC, thus EASL guidelines state that patients with noncirrhotic stage 3 fibrosis should be included in the surveillance program, although the evidence level is low.[72] The guidelines also raise the issue of optimal surveillance tool for patients with NAFLD/NASH. Obesity makes ultrasound screening more difficult in these patients. Because the use of computed tomography or magnetic resonance imaging is not cost-effective, the development of appropriate surveillance tools (serological or radiological) for this population is required.

The etiology and epidemiology of HCC are rapidly changing worldwide. This trend indicates a transition from viral to non-viral causes and an increasing incidence of alcohol- and NAFLD-related

HCC. Despite vaccination and treatment, HBV and HCV currently remain the most common etiologies in Asia and worldwide, while NASH is the fastest growing etiology of HCC in the world. To cope with this, effective cooperation between the government and academic society is necessary.

Conflicts of Interest

Ethics Statement

Funding Statement

Data Availability
Not applicable.

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Author Contribution

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