The Changing Demographics and Epidemiology of Hepatocellular Carcinoma

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KEYWORDS

• MASH • MASLD • HBV • HCV • ALD • Epidemiology • HCC

KEY POINTS

- The epidemiology of hepatocellular carcinoma (HCC) has changed considerably over the past few decades.
- Non-viral causes of HCC such as metabolic dysfunction-associated steatotic liver disease and alcohol-associated liver disease are increasing worldwide, including in the United States.
- Immigration trends may influence the epidemiology of Hepatitis B virus within the United States and subsequently increase the risk of HCC.
- Surveillance can be challenging to identify high-risk populations and warrants further research and stakeholder attention.

INTRODUCTION

Hepatocellular Carcinoma (HCC) is the most common primary liver malignancy worldwide, accounting for over 75% of all primary liver cancers.[1] In 2023, models predicted over 41,000 new cases of invasive liver cancer in the United States, along with over 29,000 deaths.[2] Although recent data suggest a promising decline in both the incidence and cancer-specific mortality of HCC in the United States, prognosis remains poor with an approximate 5-year survival rate of 21%.[3]

Over the past few years, we have witnessed significant epidemiologic shifts in risk factors for HCC due to the obesity epidemic, global migration patterns, and the coronavirus disease 2019 (COVID-19) pandemic. As the obesity epidemic is ongoing, there continues to be a shift toward non-viral hepatic disease. Global Burden of Diseases (GBD) data for 2019 showed that Hepatitis B virus (HBV) infection, Hepatitis C virus

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(HCV) infection, alcohol associated liver disease (ALD), metabolic dysfunction-associated steatotic liver disease (MASLD), and other uncommon risk factors accounted for 41%, 28.5%, 18.4%, 6.8% and 5.3% of HCC cases, respectively.[4] For comparison, in 2012, Global Cancer Observatory estimated 56% of HCC cases globally were attributable to HBV and 20% to HCV.[5]

The underlying etiologies of HCC also show considerable geographic variations (**Fig. 1**) likely due to differences in sociocultural settings, diets, genetic predisposition, and immunization practices.[6] In particular, alcohol related liver disease has the largest global heterogeneity and there is also gender variance in HCC epidemiology.[7]

A person's environment, their culture, and their exposures to viruses, alcohol, and metabolic dysfunction directly impacts their risk for HCC. This evolving landscape of HCC should inform stakeholders that a meticulous approach to prevention, screening, and treatment is needed. In this comprehensive review, we discuss HCC epidemiology including evolution of risk factors, HCC prevention, surveillance, and clinical management.

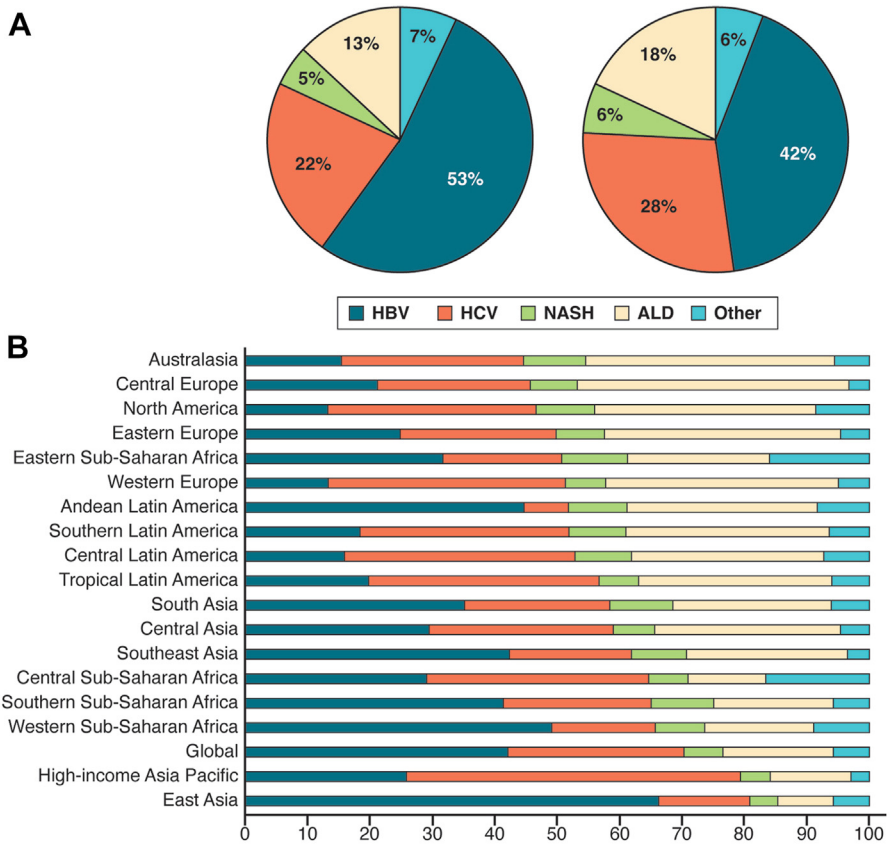

Fig. 1. Temporal and geographic variations in Hepatocellular Carcinoma (HCC) etiologies. (*A*) Distribution of etiologies in 1990 and 2019 based on Global Burden of Diseases. (*B*) Geographic variations in HCC etiologies in 2019. (*Adapted Unchanged From* Toh MR, Wong EYT, Wong SH, et al. Global Epidemiology and Genetics of Hepatocellular Carcinoma. *Gastroenterology.* 2023;164(5):766-782. https://doi.org/10.1053/j.gastro.2023.01.033; permission requested.)

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HEPATITIS B

Epidemiology

The incidence and prevalence of HBV shows considerable geographic variation. The World Health Organization's (WHO) global hepatitis strategy outlines a commitment to decreasing incidence and mortality of viral hepatitis by 90% and 65%, respectively.[8] In a 2020 WHO report, the prevalence of hepatitis B surface antigen (HBsAg) was highest in the African region (7.53%; 95% CI 5.68–10.49), followed by the Western Pacific region (5.92%, 4.87–7.26). The Americas had the lowest prevalence of HBsAg (0.53%, 0.30–1.21).[7] As a result, Africa and Asia have higher rates of HBV-associated HCC as compared to the western hemisphere.[9] The decrease in HBV prevalence in the United States is largely attributed to successful vaccination programs. Despite these trends, chronic HBV infection remains the most common cause of HCC worldwide.

Universal national immunization programs, such as those ongoing in Taiwan, are effective in reducing the incidence of HCC due to HBV and exemplify the success possible from public health policy improvements.[10] However, due to factors such as limited health infrastructure, costs, lack of health literacy, unequal access to immunization, and sociocultural determinants, the African and Asia-Pacific regions continue to lag behind in HBV eradication. These regions also comprise the vast majority of HBV-related HCC in the world.[11] The rates of preventative, diagnostic, and treatment coverage in several regions remains below WHO's 2030 target for hepatitis B elimination.[12]

Individuals with chronic HBV infection are at significantly increased risk of morbidity and mortality from liver disease. It is estimated that the lifetime risk of developing liver cirrhosis with or without HCC is up to 40% in chronic HBV carriers.[13] In addition, HBV is an oncogenic virus that can cause HCC in the absence of cirrhosis due to its mutagenic activity.[14]

Immigration Trends and Hepatitis B virus

In recent years, there has been increased migration to Western countries, which is likely to influence the HBV trends in the United States.[15] Reports suggest that immigrants comprise up to 15% of the US population, totaling approximately 44 million individuals.[16] On a worldwide scale, the number of international migrants increased in 2022 to 281 million from 244 million in 2015.[16,17] In the United States, population-based prevalence estimates of HBV from the National Health and Nutrition Examination Survey (NHANES) are challenging to interpret given limitations related to English proficiency, hesitation to acknowledge foreign-born status, and diversity in immigrants' country of birth.[18] Razavi-Shearer and colleagues used a dynamic Markov model to determine HBV prevalence and estimated approximately 1.8 million HBV infections (95% uncertainty interval, 1.3–2.6) in 2020, higher than the NHANES survey which estimated the prevalence to be 660,000 for a period ranging from January 2017 to March 2020.[18,19] Of these, 76% (1.4 million) were estimated to be among immigrants. The study authors found that approximately 74% of all chronic HBV-positive immigrants to the United States are from 5 regions: Southeast Asia (465,300), East Asia (208,600), Caribbean (144,500), Sub-Saharan West Africa (122,800), and South Asia (98,700).[18] The estimated prevalence of HBV positivity among immigrants from non-traditional Asian countries such as Myanmar (11,400 in 2020), Uzbekistan (10,700), Afghanistan (5,000), Nepal (3,500), and Kazakhstan (1,400), among others, is also notable.[18]

Interestingly, Mongolia is estimated to have the highest incidence of HCC in the world with 86 cases per 100,000 inhabitants. The prevalence of HBV in the Mongolian population is around 8.1% to 11.8% (based on prior studies).[20,21] A large number of young adults were also reported to be unaware of their viral infection status (HBV

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and/or HCV).[21] When comparing 190 cases of HCC in Mongolia to other global cases, researchers found patients had differences in molecular signatures, high mutational burden, and genotoxic environmental factors.[22]

Potential Impact of Immigration Trends for Hepatocellular Carcinoma in the United States

A report from a tertiary care center showed that while HCV was the most common underlying liver disease in the US-born population compared with the immigrant population (83% vs 52%, $P<.001$), HBV was significantly more common among immigrants (29% vs 4%, $P<.001$).[23] Analyses of the Surveillance, Epidemiology, and End Results (SEER) registry have also shown that a patient's birth country influences age at presentation. For HCC in the US, birth in West Africa, Central/South Africa, Oceania, or East Africa is associated with both very-early onset (age < 40 year old at diagnosis) and early-onset (age < 50 year old at diagnosis) HCC. This association has been attributed to an earlier age at acquisition of HBV (or HCC) infections in these countries, along with the synergistic interaction between HBV infection and common environmental exposures such as aflatoxin.[24]

Accounting for immigration trends is essential in recognizing the impact of chronic HBV as a risk factor for HCC along with optimizing disease surveillance, especially for immigrant populations where the prevalence of HBV may be underestimated. AASLD guidelines from 2023 suggest a surveillance program for HBV positive patients with risk factors such as family history of HCC, males greater than 40 year old from endemic counties, females greater than 50 from endemic countries, or birth in Africa.[25]

HEPATITIS C

Epidemiology

The prevalence of HCV infection globally is around 0.75% (95% CI, 0.60–0.98), with the Eastern Mediterranean region having the highest prevalence (1.64%; 1.36–1.81), followed by the European region (1.34%; 1.07–1.48). HCV prevalence is relatively lower in the Americas (0.47%; 0.40–0.54) and the Western Pacific region (0.49%; 0.42–0.70).[7] HCV is responsible for approximately 28.5% of HCC cases worldwide as per GBD estimates from 2019.[4] Recent data suggest that only 11 countries are on track to meet the WHO goal of 80% reduction by 2030.[26] It is estimated that 20% of chronic HCV-infected individuals develop liver cirrhosis within 20 to 30 years. Patients without cirrhosis can still be at risk for HCC due to non-linear fibrosis.[27] The rate of development of HCC in HCV cirrhosis is up to 5% per year.[28] Concurrent liver disease, lifestyle factors, obesity, and diabetes mellitus are major risk factors for the development of HCC in patients with chronic HCV infection.[29] HCV-related HCC development is mediated by interactions with host immune response in a stepwise process that often spans over multiple decades.[29]

Of note, HCV viral genotypes confer differential risks of developing cirrhosis and HCC. Results from a large HCV clinical registry have found that genotype 3 is associated with an increased risk as compared to genotype 1.[30] HCV genotype 1 has the highest prevalence in the United States (approximately 75%), followed by genotypes 2 and 3.[31] Genotype 1 remains the most prevalent genotype worldwide (49.1%) followed by genotype 1 (17.9%). Genotypes 4 and 5 are more commonly found in lower-income Middle Eastern countries such as Egypt or Iraq (**Fig. 2**).[32] A similar distribution of HCV genotype prevalence was reported by the Polaris Observatory HCV Collaborators.[33] This viral heterogeneity complicates prevention strategies and precludes effective vaccine development.

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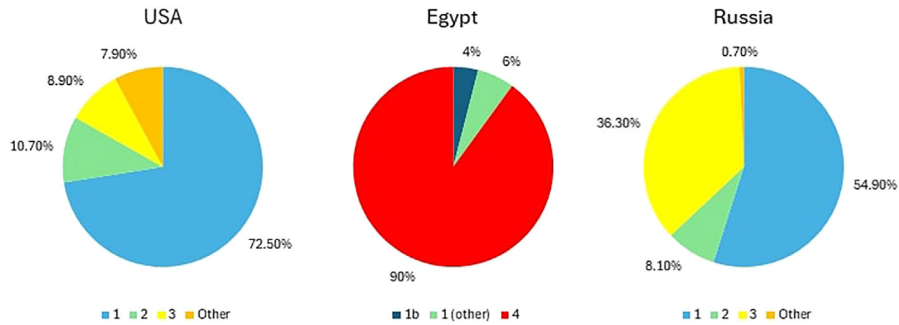

Fig. 2. Varying proportions of Hepatitis C Virus genotype prevalence across the US, Egypt, and Russia. (*Data from* Blach S, Zeuzem S, Manns M, et al. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *The Lancet Gastroenterology & Hepatology.* 2017;2(3):161-176. https://doi.org/10.1016/S2468-1253(1630181-9.)

Hepatitis C Virus Treatment, Sustained Virologic Response, and Hepatocellular Carcinoma Risk

The advent of direct acting antiviral (DAA) therapy in 2013 led to a reduction of liver disease related mortality and HCC occurrence due to HCV in the last decade.[34] Commonly utilized first-line DAA regimens include glecaprevir/pibrentasvir, elbasvir/grazoprevir, and sofosbuvir-based regimens.[35] Sustained virological response, defined as a negative HCV PCR (viremia) at 12 weeks or more after the completion of DAA treatment, can be achieved in over 94% of patients, including those with hepatic decompensation.[36,37] When patients achieve sustained virologic response (SVR), their risk of HCC is significantly reduced along with regression of cirrhosis.[38,39] Moreover, studies show that DAA regimens improve fibrosis scores in over 60% of patients over a 12-week period irrespective of clinical or virological factors.[40] A retrospective analysis of 797 patients found that achieving SVR reduces overall mortality (HR, 0.29).[41]

It is difficult to predict which patients develop HCC despite achieving SVR with DAA therapies. Ravaioli *and colleagues* explored liver stiffness measurement (LSM) changes in 139 patients with HCV-related cirrhosis. A change in LSM of less than 30% (vs $\geq$ 30%), Child-Turcotte-Pugh-B score, and previous history of HCC were significantly associated with an increased risk of HCC development after DAA treatment.[42] In a cohort with 2-year follow-up, Peleg and colleagues showed that patients with baseline ultrasonographic liver steatosis (LS) exhibited an increased risk of all-cause mortality and HCC.[43] This study also showed that patients with advanced fibrosis also trended toward an increased risk of HCC development and mortality.[43] A Japanese group found age greater than 75 years and post-treatment AFP values above 6 ng/mL were independently associated with HCC occurrence following DAA treatment.[44] Pre-treatment diabetes mellitus is another strong risk factor for HCC development after HCV cure, along with a higher fibrosis-4 index.[45,46]

Alcohol consumption acts synergistically with HCV in progression toward cirrhosis and HCC development.[47] The annual incidence of HCC remains higher (1.01%, 95% CI, 0.83–1.19) among patients with SVR who report alcohol use (0.72%; 95% CI, 0.54%–0.91%).[38] Notably, SVR does not completely nullify the risk of developing HCC (**Fig. 3**) and the absolute risk of developing HCC remains high (0.90 per 100 person-years).[38] The incidence of HCC is higher in patients with cirrhosis and SVR (1.82–1.97 per 100-person years) than in patients without cirrhosis who experience

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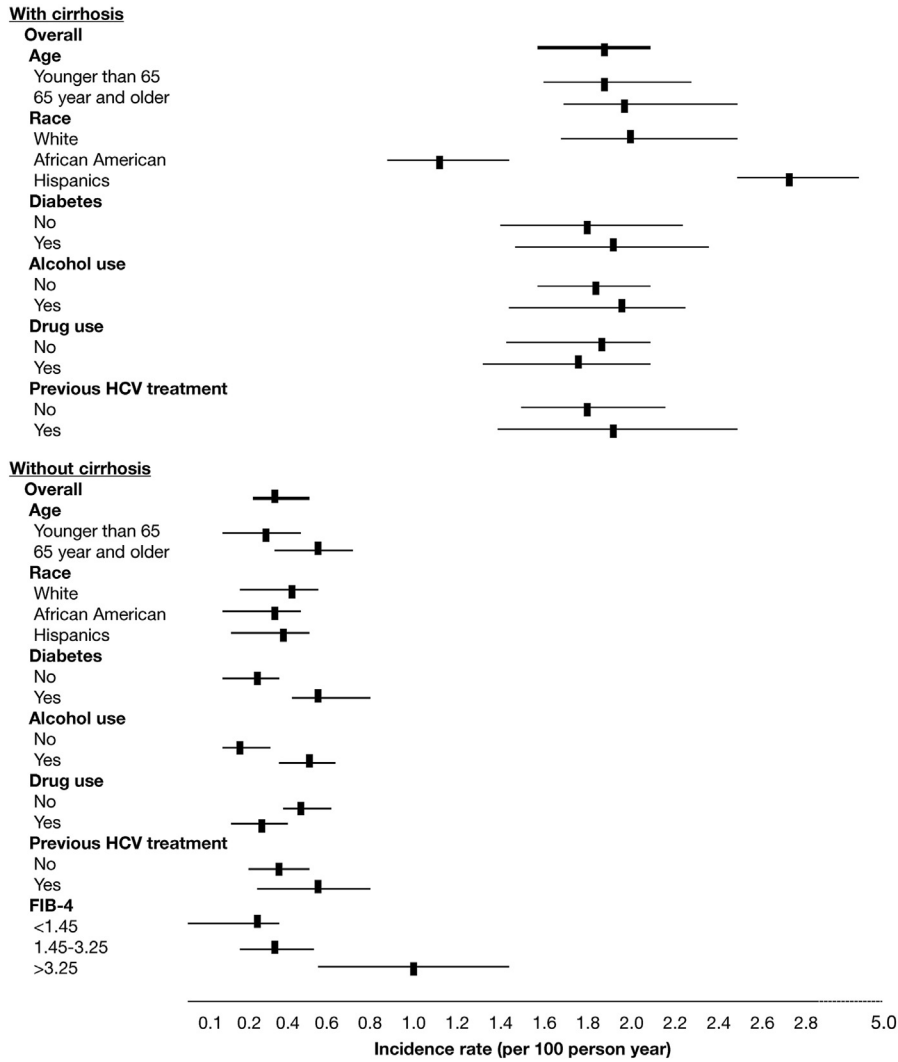

Fig. 3. Annual incidence of HCC in patients with SVR divided by the presence of cirrhosis at baseline. (*Adapted Unchanged From* Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of Hepatocellular Cancer in HCV Patients Treated With Direct-Acting Antiviral Agents. *Gastroenterology.* 2017;153(4):996-1005.e1. https://doi.org/10.1053/j.gastro.2017.06.012; permission requested.)

treatment failure (0.87 per 100-person years).[38,48] Although patients without cirrhosis are at a lower risk of developing HCC after SVR, patients with F3 fibrosis present with staging difficulties and decisions regarding surveillance remain challenging.[49] Among these patients with cirrhosis and SVR, the incidence of HCC does decrease over time and is the lowest in younger patients and those with compensated cirrhosis.[50] Current surveillance guidelines from the AASLD recommend against routine HCC surveillance in patients with HCV post-SVR without cirrhosis.[25] However, in certain high-risk populations, it is reasonable to consider more proactive screening strategies personalized to each patient's risk based on modifiable factors and lifestyle factors.

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METABOLIC DYFUNCTION-ASSOCIATED LIVER DISEASE

Epidemiology

MASLD, previously known as nonalcoholic fatty liver disease, is an umbrella term encompassing simple steatosis to eventual decompensated liver disease.[51] Patients with hepatic steatosis plus at least 1 cardiometabolic risk factor are diagnosed with MASLD. MASLD affects millions of people worldwide, with a global prevalence of approximately 32% (95% CI, 29.9–34.9).[52] The prevalence of MASLD in the United States is approximately 47.8% (95% CI, 25.9–69.7).[52] Forecasts predict global prevalence to escalate to as high as 55% by 2040, predominantly due to poor lifestyle choices.[53] Additionally, the incidence (70.8 per 1000 person-years vs 29.6 per 1000 person-years) and prevalence (39.7% vs 25.6%; $P<.0001$) of MASLD are considerably higher in men.[52]

The presence of MASLD increases an individual's risk of progression to cirrhosis. It is estimated that up to 5% of MASLD progresses to metabolic dysfunction-associated steatohepatitis (MASH) with advanced fibrosis or cirrhosis.[54] MASLD also has the potential to affect an individual's overall quality of life. According to a population-based study, 22% of patients with MASLD rated their health as poor or fair compared to 10% of healthy controls.[55]

An excessive intake of calories, carbohydrates, and fats leads to lipogenesis and the eventual occurrence of MASLD. Obesity, along with insulin resistance, leads to chronic inflammation, altered lipid metabolism, and a chronic low-grade inflammatory response which fosters a carcinogenic environment (**Fig. 4**).[56]

Growing Prevalence of Metabolic Dysfunction-Associated Steatotic Liver Disease Associated Hepatocellular Carcinoma

MASLD continues to be the fastest growing cause of HCC in the United States for patients awaiting liver transplant.[57] Since the early 2000s, the prevalence of HCC in liver transplant candidates with MASH has increased more than 10-fold.[58] In a European

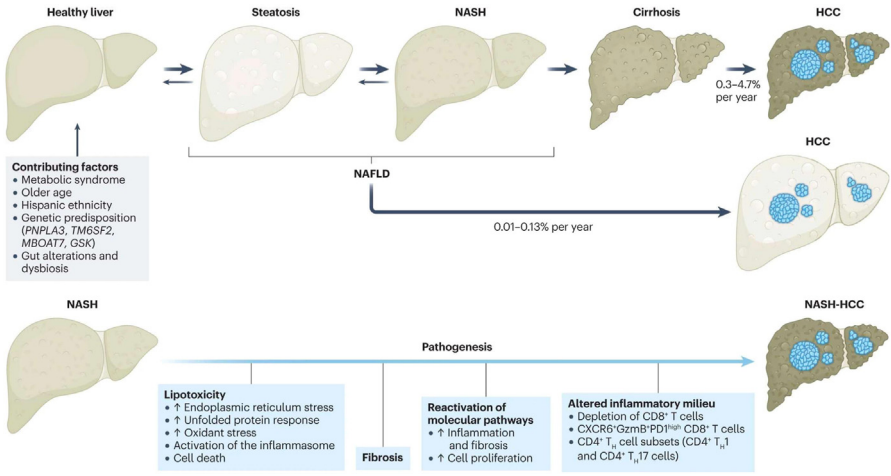

Fig. 4. Mechanisms behind the pathogenesis from a healthy liver to nonalcoholic fatty liver disease (NAFLD) and subsequent HCC. NB: NAFLD is the older name for MASLD. (*From* Llovet JM, Willoughby CE, Singal AG, et al. Nonalcoholic steatohepatitis-related hepatocellular carcinoma: pathogenesis and treatment. Nat Rev Gastroenterol Hepatol. 2023;20(8):487-503. https://doi.org/10.1038/s41575-023-00754-7.)

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study from 2019, type 2 diabetes was the strongest independent risk factor for HCC in patients with MASLD.[59]

Obese men have an increased risk of HCC-related mortality compared to obese women. Obesity confers roughly a 2-fold increased risk of HCC-related mortality compared to overweight individuals (BMI 25–29.9 kg/m^2).[60] A BMI greater than 30 kg/m^2 doubles the risk of HCC, and a BMI greater than 35 kg/m^2 confers a 4-fold increased risk of HCC, independent of co-morbid conditions.[58]

Prior data suggested around a 2% annual risk of MASH-cirrhosis progressing to HCC. While this progression is multifactorial, major contributors appear to be immune milieu, presence of high-risk germline mutations (such as *PNPLA3*), gut microbiome, and risky lifestyle behaviors.[56] Despite cirrhosis being a risk factor for MASH-HCC development, MASH-HCC can develop in the absence of cirrhosis in up to 40% of cases.[61]

Non-invasive testing including panels such as the Enhanced Liver Fibrosis panel (hyaluronic acid, PIIINP, and TIMP-1) can be helpful to risk stratify patients for disease progression.[62] Transient elastography (FibroScan) is also used to evaluate liver stiffness and provide insight into fibrotic burden. Moderate liver stiffness is independently associated with the development of HCC in patients with MASLD.[58] Due to high costs, computed tomogrpahy, and MRI should be used judiciously in high-risk populations, but may be necessary in this population as ultrasound can be technically challenging in obese individuals.[63] For patients with MASLD without cirrhosis, routine surveillance for HCC is not recommended, irrespective of the presence of advanced fibrosis.[25]

The American Gastroenterological Association advises lifestyle modification to achieve weight loss for all patients with MASLD.[62] Glucagon-like peptide-1 agonists have a promising role in decreasing fatty deposition, inflammation, and fibrosis in MASLD.[64] Recent data from the phase III MAESTRO-NASH trial have shown that Resmetirom, an oral, liver-directed, thyroid hormone receptor beta selective agonist, was superior to placebo with respect to MASH resolution and improvement in liver fibrosis by at least one stage.[65]

ALCOHOL ASSOCIATED LIVER DISEASE

ALD is the most common type of chronic liver disease worldwide. Chronic consumption causes a progression in ALD from alcohol associated fatty liver to alcohol associated steatohepatitis (ASH), a condition involving hepatic inflammation. Prolonged ASH can precipitate fibrosis, cirrhosis, and increases one's risk for HCC development. Alcohol-induced hepatic carcinogenesis is due to various mechanisms including: increased acetaldehyde, elevated CYP2E1, increased reactive oxygen species, chronic inflammation, and epigenetic alterations.[66,67]

Brief Epidemiology of Alcohol-Associated Hepatocellular Carcinoma and Pitfalls

The 10-year cumulative risk of HCC in alcohol-associated cirrhosis is approximately 9%.[68] Studies have also suggested that the risk of alcohol-associated HCC increases with increased levels of consumption (**Fig. 5**).[69] Alcohol associated HCC is also linked with imperfect surveillance and poor patient compliance which often leads to delayed diagnosis.[67] Furthermore, the epidemiology of ALD-related HCC is poorly understood due to limited national registries, undisclosed alcohol use, disease coding changes, and a frequent lack of ICD coding distinction between HCC and other primary liver cancers.[67] In addition to being a major risk factor for the development of cirrhosis and HCC, alcohol interacts synergistically with underlying etiologies such as MASLD or HCV, exponentially increasing HCC risk.

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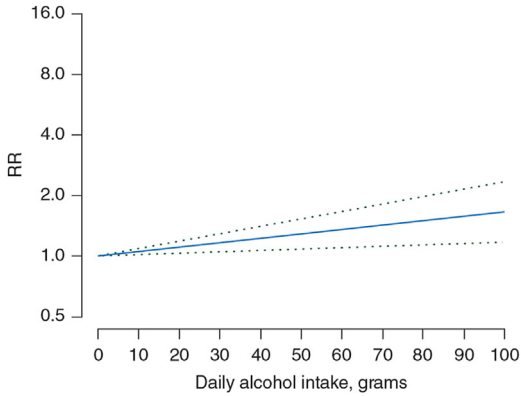

Fig. 5. A relative risk function (with the corresponding 95% CI) describing the best-fitting dose–response relationship between alcohol consumption and the risk of liver cancer. (*Adapted Unchanged From* Turati F, Galeone C, Rota M, et al. Alcohol and liver cancer: a systematic review and meta-analysis of prospective studies. *Annals of Oncology.* 2014;25(8):1526-1535. https://doi.org/10.1093/annonc/mdu020; permission requested.)

Global Trends in Alcohol Consumption

Global alcohol use has increased significantly over the past 2 decades and is expected to rise in the future leading to significant liver related morbidity and mortality including HCC.[70,71] In particular, alcohol per capita consumption rose steadily in the Western Pacific region and the Southeast Asian region. Notably, Europe witnessed a fall in alcohol consumption which may be attributed to higher costs and increased taxation.[70] In 2017, among those that drink alcohol, Manthey and colleagues found approximately 20% of adults consumed at least 60 g of alcohol on one occasion within a 30-day period (deemed 'heavy episodic drinking'). This figure represents an increase from the 18.5% reported in 1990 and is projected to rise to 23% by 2030.[72]

Resurgence of Alcohol-Associated Liver Disease

Global trends in alcohol-associated HCC are linked with trends in ALD. A meta-analysis revealed an increase in the global prevalence of ALD from 4.6% in the early 2000s (2000–2010) to 5.6% during the subsequent years to 2021 (2011–2021).[73] Researchers noted the impact of the COVID-19 pandemic in exacerbating alcohol use and mental health problems across the globe.[74] A retrospective review indicated a significant increase in the number of patients both awaiting and receiving liver transplants for acute alcohol-associated hepatitis during the pandemic, attributed by the authors to high-risk alcohol use.[75]

Recent GBD data suggest that alcohol use was the second-fastest growing cause of liver cancer deaths after MASLD. Age-standardized death rates of liver cancer due to alcohol consumption increased from 1.08 per 100,000 individuals in 2010 (95% uncertainty interval, 0.90–1.29) to 1.10 (95% UI, 0.89–1.33) in 2019.[76] If current trends persist, the incidence of alcohol-associated HCC is predicted to increase from 1.1 (per 100,000 person-years) in 2019 to 2.0 in 2040.[77]

Utilizing accessible effective, yet underutilized pharmacotherapeutics such as naltrexone and acamprosate can greatly assist patients in limiting their exposure to the toxic effects of alcohol.[78,79] Early engagement with a health care team allows for timely intervention and prevention of the deleterious effects of alcohol associated

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hepatitis and eventual alcohol-related decompensated cirrhosis.[80] In patients without decompensated cirrhosis, abstinence further lowers the risk of HCC, highlighting the importance of timely counseling and preventive interventions in this population.[81]

SUMMARY

The landscape of the underlying etiologies and global epidemiology of HCC has changed considerably over the past few decades. The prevalence of viral hepatitis has reduced significantly in developed countries like the US, largely owing to successful immunization programs, educational outreach, and antiviral therapies. However, globally, efforts are insufficient to meet the WHO's targets for the elimination of hepatitis C by 2030.

Global immigration trends will continue to impact the epidemiologic landscape of viral hepatitis and HCC in the United States. Policymakers must be aware of the challenges of under-reporting and ensure processes for adequate surveillance and treatment in these patients. Furthermore, in patients with HCV cirrhosis, curative treatments do not eliminate the risk of HCC and models to optimize surveillance in high-risk individuals are warranted.

In addition, the obesity epidemic resulted in increased prevalence of MASLD which is one of the fastest growing causes of HCC in the developed world. Challenges associated with HCC surveillance in patients with MASLD include identifying those without cirrhosis who are at high risk for cancer development.

A resurgence of ALD, likely due to an increase in global per capita alcohol consumption, has occurred in the last 2 decades. The COVID-19 pandemic and associated stressors have intensified alcohol use disorder and subsequent morbidity and mortality, including liver related consequences. The utilization of psychotherapy, guided interventions and pharmacotherapy in this population can help curtail this resurgence and reduce the incidence of ALD-associated HCC.

The changing epidemiology of HCC brings along several important challenges for clinicians, policymakers, and other stakeholders. Effective public policy initiatives, culturally sensitive outreach, and ongoing educational platforms are key in these efforts.

CLINICS CARE POINTS

- The epidemiology of HCC has changed considerably over the past few decades with non-viral causes of chronic liver disease like MASLD and ALD becoming increasingly prevalent worldwide.
- HBV prevalence remains high in several developing nations. Increasing global immigration and migration from these regions into the United States can influence the underlying landscape of viral hepatitis epidemiology and subsequently HCC.
- Prevalence estimates, eradication efforts, and HCC surveillance can be challenging in immigrant populations, further contributing to the challenges associated with HBV prevention and treatment.
- HCV cure does not eliminate the risk of HCC in patients with cirrhosis and identifying high-risk individuals is warranted.
- There has been a recent resurgence of ALD, likely compounded by the stressors linked to the COVID-19 pandemic. Attention to preventive strategies and early intervention are key to reducing ALD related morbidity and mortality.

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- The global prevalence of obesity, insulin resistance, and subsequently MASLD is increasing. MASLD is becoming a leading cause of HCC, especially in developed countries. Improved biomarkers are needed to identify high risk groups for HCC development in patients with MASLD without cirrhosis.

DISCLOSURE

R. Gujarathi: None; J.A. Klein: None; C-Y. Liao: Consultant for: AstraZeneca, Genentech, Histosonics, Incyte, Ipsen, QED, Transthera, Boston Scientific. Speaker for: AstraZeneca, Incyte. A. Pillai: On the medical advisory board of Exelixis, Genentech, AstraZeneca, Eisai Inc. and on the safety advisory board for Replimune.

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