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MINIREVIEWS

Epidemiologic and socioeconomic factors impacting hepatitis B virus and related hepatocellular carcinoma

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Abstract

Chronic Hepatitis B is a highly prevalent disease worldwide and is estimated to cause more than 800000 annual deaths from complications such as cirrhosis and hepatocellular carcinoma (HCC). Although universal hepatitis B vaccination programs may have reduced the incidence and prevalence of chronic hepatitis B and related HCC, the disease still imposes a significant healthcare burden in many endemic regions such as Africa and the Asia-Pacific region. This is especially concerning given the global underdiagnosis of hepatitis B and the limited availability of vaccination, screening, and treatment in low-resource regions. Demographics including male gender, older age, ethnicity, and geographic location as well as low socioeconomic status are more heavily impacted by chronic hepatitis B and related HCC. Methods to mitigate this impact include increasing screening in high-risk groups according to national guidelines, increasing awareness and health literacy in vulnerable populations, and developing more robust vaccination programs in under-served regions.

Key Words: Hepatitis B; Epidemiology; Hepatocellular carcinoma; Socioeconomic status; Healthcare disparity; Hepatitis B vaccine

Core Tip: While many studies in the past have analyzed the impact of various epidemiological and socioeconomic factors on viral hepatitis and hepatocellular carcinoma (HCC), this minireview is the first to adopt a global perspective in highlighting the impact of both epidemiologic and socioeconomic factors on current trends in chronic hepatitis B and related HCC. We highlight trends in incidence, prevalence and mortality of chronic hepatitis B seen throughout the world in the past few decades and the disparity in healthcare distribution and outcomes between different populations.

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INTRODUCTION

In 2019, the World Health Organization (WHO) estimated the worldwide prevalence of chronic hepatitis B virus (HBV) to be around 296 million with the incidence of new HBV infection to be 1.5 million each year. HBV is more prevalent with high burden of disease in the regions of Africa, Western Pacific and South-East Asia compared to North America and Europe. Furthermore, fewer people in the African and South-East Asian regions knew about their HBV status and had access to treatment compared to the latter regions[1].

Hepatocellular carcinoma (HCC) in unsuspected HBV patients is a major cause of increased morbidity and mortality in low-income countries with limited resources[2,3]. While it may be too early to see the true impact of the global HBV vaccination initiative led by the WHO or treatment efforts for HBV-related HCC, evidence thus far demonstrates decreased burden of HBV and HCC in children and suggests treatment with antivirals can reduce HCC risk in some patients[4-8]. There continues to be great disparity in access to vaccines, treatment, and screening programs worldwide, however. Even where there is access, the risk of HCC in treated chronic HBV is not fully mitigated[9,10]. While concomitant liver diseases are certainly at play including co-infection with hepatitis C, aflatoxin exposure, metabolic syndrome, and alcohol use disorder, chronic HBV-related HCC has a significant global disease burden that disproportionately impacts people of different regions and demographics[9,11]. The aim of this review is to examine the impact of epidemiologic and socioeconomic factors on chronic HBV-related HCC from a global perspective. Strategies to address the resulting disparities in disease outcomes will also be discussed.

DEMOGRAPHIC FACTORS

Geographic variations

There is significant global variation in the prevalence of chronic HBV between regions. As a result, the incidence and prevalence of HBV related HCC are also quite variable between regions and correlate with rate of HBV infection[12]. About 50%-80% of HCC can be linked to HBV worldwide, and the high-risk HCC regions represent 80% of the global burden of HCC[13]. Regions such as Africa, Southeast Asia, and the Western Pacific, are considered high-risk HCC regions owed partially due to high seroprevalence of chronic HBV which is estimated at 5%-10%. On the contrary, North America and Western Europe are low-risk HCC regions with an HBV prevalence of < 1%. The Middle East and the Indian subcontinent are intermediate-risk regions with HBV prevalence of 2%-5%[14]. Data illustrating the geographic distribution of chronic HBV by prevalence is seen in Table 1 and Figure 1.

Asia and Africa

Prevalence of HBV in Asia and Africa within high-risk regions is not uniform. In Africa, particularly West Africa and Sub-Saharan Africa, complications of chronic HBV including cirrhosis and HCC are frequent and fatal due to a relative lack of vaccination, surveillance and treatment[15]. Sub Saharan Africa had an estimated vaccination rate of less than 10% and fewer than 1% of HBV infections were diagnosed in 2019[9].

In East Asia, China has a high prevalence of HBV-related HCC, estimated to be 50% of the world's burden of HCC. Mongolia has the highest incidence rate of HCC in the world at 93.7 per 100000 with HBV being the predominant risk factor[9]. However, countries of low HCC incidence also exist in the Asia-Pacific region such as Japan, India, Singapore, and Pakistan. Interestingly, Japan has a low incidence of HBV where hepatitis C virus (HCV) is the major contributor of HCC, estimated to account for 80%-90% of cases[11,14,16].

Table 1 Geographic distribution of Chronic hepatitis B virus by estimated disease burden in 2019

Geographic region[22,40]	People living with hepatitis B infection
African region	82.3 million (62.1-114.7 million)
Region of the Americas	5.4 million (3.1-12.0 million) (2.1 million in Latin America and the Caribbean)
Eastern Mediterranean region	18.2 million (14.4-23.8 million)
European region	13.6 million (10.2-22.1 million)
South-East Asia region	60.5 million (45.3-120.9 million)
Western Pacific region	115.7 million (95.2-141.9 million)

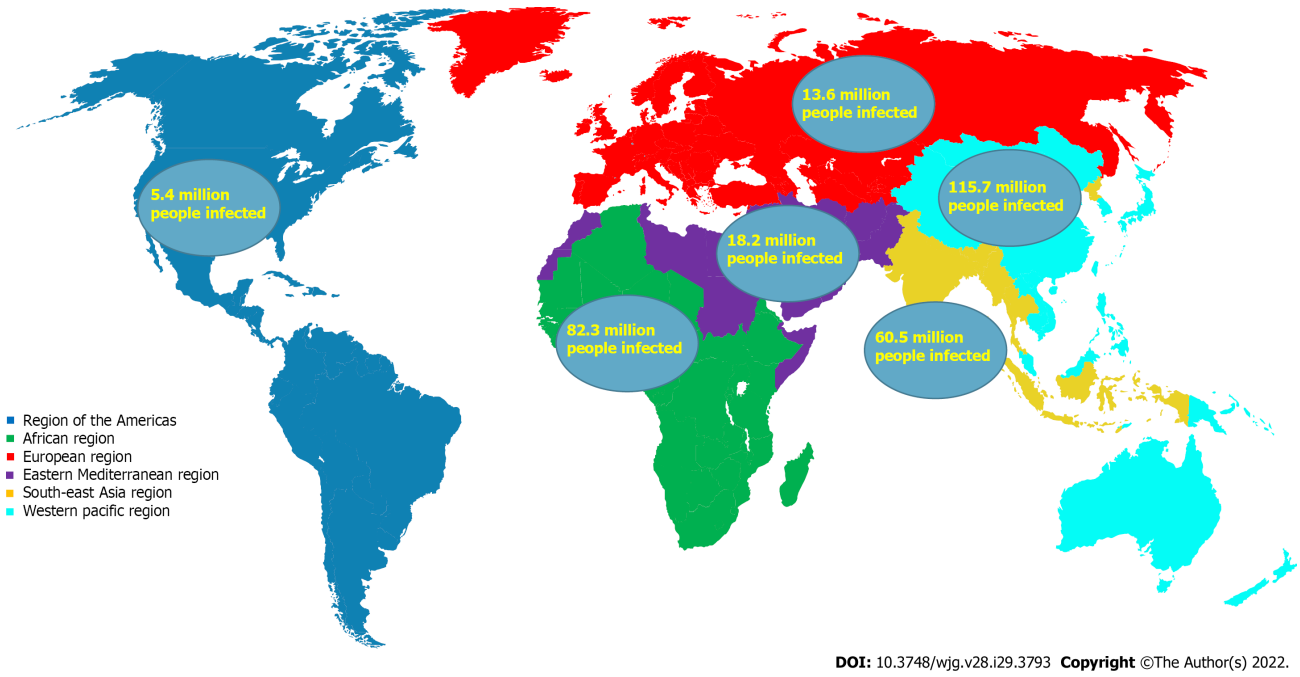

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Figure 1 Geographic distribution of chronic hepatitis B virus.

Data from Asian nations such as India, China, Thailand and Nepal show that there are evident disparities in HBV prevalence within population sub-groups[17,18]. Surveys of the Tibetan population in Nepal's Kathmandu valley showed prevalence of chronic HBV of 10%-20% compared to the overall prevalence of 0.9% in Nepal[18]. The general population of China has an estimated HBV prevalence of 6.89% while Western provinces have a higher prevalence at 8.92%[19]. The hill tribe of Chiang Rai province in Thailand see a significantly higher prevalence of chronic HBV at 26.6% while the overall prevalence in Thailand is 5.1%[17,20]. Although Southeast Asia as a region has a higher prevalence of HBV infection at 3.0%, there are variations in prevalence between ethnicities within the region. Given the relatively high prevalence rate of chronic HBV infection in Southeast Asia compared to Europe and the Americas, the incidence of liver cancer being highest in these regions is not surprising[11,21]. Some explanations for the disparities seen in the various regions and ethnic groups include unequal access to vaccines, limited health care programs, lack of health literacy, and elements of culture and religion that also serve a role[17,19,21].

United States

Immigration from endemic countries is the main contributor to chronic HBV cases in the United States, which has a prevalence rate of 0.5% compared to 3.8% globally[21]. An estimated 70% of HBV infections in the United States are among foreign-born individuals with an estimated 730000 to 2.2 million living with chronic HBV[22]. Screening studies of foreign-born immigrants from Africa, the Middle East, and Asia have shown a higher chronic HBV prevalence rate of 10%-15% compared to 0.27%-0.50% for the general population[11,12,23,24]. Chronic HBV infection is disproportionately higher amongst Asian Americans in the United States[25]. Asian Americans comprise roughly 5%-6% of the population in the United States but 50% of the cases of chronic HBV[22].

Studies have also shown ethnic variation in HBV-related HCC within the United States, owing to differing sizes of immigrant populations from endemic countries. While rates of HCC in Asian and Pacific Islanders, once elevated are now declining, the incidence of HCC in Hispanics, Whites and African Americans continues to increase, driven mainly by HCV and non-alcoholic steatohepatitis (NASH) related cirrhosis[7,23,26-28]. Southern and Western states have the highest incidence rates of HCC in the United States[28]. While Asian Americans have the lowest mortality rates from HCC of all ethnicities, the highest mortality rates are seen in African Americans[29,30]. This apparent disparity may be partially explained by the etiology of HCC which include alcohol use disorder and HCV related cirrhosis, as well as health care disparities and access to quality care among African Americans. Recent studies show a disparity even after liver transplantation in patients with HCC, with African Americans consistently having worse survival than Asian Americans and White American patients[31].

Europe

Western Europe, like the United States, has a growing diversity in its population. Most chronic HBV infections in Western European countries are due to migrant populations, with an HBV prevalence estimated to be around 4% for migrant populations and < 1% for the general population[23,27]. There is also a greater prevalence of cirrhosis and HCC in the foreign-born population[32]. A population-based study of HCC in England found a higher proportion of HCC in non-white ethnicities, particularly due to viral hepatitis-related HCC[33]. Similar findings are reported in studies of other low HCC risk countries such as Austria, Finland, Netherlands, Germany, the United Kingdom and Denmark in which migrant populations are over-represented in cases of chronic HBV and HCC[32,34].

Latin America

There is a reported heterogeneous distribution in chronic HBV prevalence amongst Latin American countries. Owed to variation in the endemicity of HBV and underreporting, some studies report an estimated 7-12 million people infected in Central and South America and the Caribbean[35]. In contrast, a report by the Pan American Health Organization and the WHO in 2016 suggested chronic HBV seroprevalence in Latin America being 0.33% with an estimated 2.1 million infected in the general population. However, the variation in HBV serum antigen (HBsAg) seroprevalence ranged from 0.20% to 13.55% among the numerous countries[36].

In the majority of Latin America, HCV and alcoholic liver disease are the leading causes of HCC. HBV is more endemic to certain countries such as Brazil, Argentina, and Peru.

Systematic reviews and retrospective studies have shown HBV-related HCC accounting for 12%-14% of HCC in South and Central America with the countries Peru and Brazil having 20%-60% of their HCC cases related to HBV infection[37-39].

Although Latin American countries are more varied in HBV prevalence and range from low to high prevalence, overall HCC risk and burden is similarly as low as the rest of the Americas in a global context[11,36].

Gender

Chronic HBV has a greater prevalence in males than females across all geographic regions[13]. Males also have a greater incidence, prevalence, and mortality from HCC than females across geographic location and age; studies have reported a 2 to 3 times increased risk of developing HCC in males compared to females[26,27,40,41].

Regions of higher chronic HBV prevalence such as sub-Saharan Africa and Southeast Asia, tend to also have a higher male to female ratio of HCC incidence. In the United States, both sexes have shown a trend of rising incidence rates of HCC since 1975, with HBV estimated to account for 10%-15% of HCC cases[42]. The gender disparity is not completely understood but is believed to be partially due to many overlapping risk factors that are more common in males, including alcoholism, diabetes, viral hepatitis, and tobacco use[43]. In the United States, heavy alcohol usage and tobacco use is much more common in males with both being independent risk factors for incidence of HCC[43,44]. In contrast, metabolic syndrome is more common in women, with one retrospective study reporting it accountable for 32% of HCC burden in the United States[27,44].

Despite controlling for other risk factors, male sex continues to remain an independent risk factor for HCC. Studies have linked higher testosterone levels to greater incidence of HCC in chronic HBV patients and estrogen replacement therapy to reduced risk of developing HCC[42,45,46]. Serum testosterone level has been associated with upregulated inflammatory activity while estrogen has shown to have an anti-inflammatory effect by inhibition of the NF-kB pathway[46-48]. Estrogen may be protective against development of HBV-related HCC through decreasing HBV RNA transcription which could explain higher viral loads seen in male carriers of HBV[12,47]. However, studies have failed to demonstrate a benefit in survival from hormonal therapy such as flutamide, an anti-androgen, and leuprorelin, a gonadotropin-releasing hormone agonist which has anti-androgen effects[48].

Age

The average age of chronic HBV patients has continued to increase over time. A study comparing

chronic HBV patients derived from an insurance claims database of Medicaid and Medicare patients found that the median age had risen from 44.1 to 50.2 years for Medicaid patients and 48.1 to 51.8 for Medicare patients[49]. This trend has also been seen in studies from other countries. A large territory-wide cohort study conducted in Hong Kong found the mean age for Chronic HBV had increased from 41 in 2000-2004 to 55 in 2014-2017[50]. Chronic HBV is now presenting at an older median age due to longer life expectancy, under diagnosis of HBV, under screening, and delayed treatment[21,51]. There is also improved vaccine-induced immunity in the 20-49 years age group which is predicted to cause a continual upward shift in the median age of diagnosis[49].

In populations at low risk for HBV infection, such as in Western Europe and the United States where HBV in not endemic, HCC is rarely seen before the fourth decade of life with a mean age of diagnosis around 65 years[12]. In contrast, endemic regions such as Southeast Asia and sub-Saharan Africa, where > 80% of HCC cases occur, have mean ages of diagnosis about one decade earlier[42]. China has a mean age of diagnosis of HCC around 55-59 years[12]. In countries in Sub-Saharan Africa, mean age of diagnosis of HCC is 35-50 years, and found to be almost 20 years later in those Black Africans who migrate from a rural to city setting[12,52].

With the advent of the HBV vaccine in 1981, and the universal vaccination programs that began in the 1990s, there was a new focus on vaccination of newborns. As of 2020, 190 WHO member countries vaccinated newborns as part of their routine vaccination schedules, and global coverage with all 3 doses of HBV vaccine was estimated to be 83%[53]. This campaign also included recommendations to vaccinate high-risk adult populations, adolescents who had missed immunization, and advocated for societal awareness of the risks and consequences of HBV[22]. Asian males who are HBV carriers continue to present with HCC at a relatively young age[54]. This may be related to viral factors such as genotype. Genotype B is more commonly seen in the Asian demographic and has been associated with onset of HCC in patients under 50 years of age, with one study from Taiwan finding that more than 90% under 35 years of age had genotype B HBV[47,55]. Genotype C is associated with the highest risk of developing HCC in patients aged > 50 years[56]. Genotype F has been seen in Alaskan Native populations to have the greatest risk of developing HCC at a lower median age, with the annual incidence rate amongst men at 387/100000 and 63/100000 for women[57]. In contrast, genotypes A, D are less frequently associated with development of HCC and more common in North American and European populations[58].

Socioeconomic status

Patients belonging to low socio-economic status are at significant disadvantage due to low health literacy, limited healthcare resources and access-including lack of insurance or ability to pay for care, especially for care of preventable diseases such as HBV. Hepatitis B is very infectious as it can be transmitted by contact with blood or bodily fluids, sexual intercourse and vertically from mother to baby. Vertical transmission is the most common mode of transmission in the developing world and can be dramatically reduced by HBV vaccination and use of anti-viral medications during third trimester [7]. Horizontal transmission seems to be more common in low prevalence regions[13,22]. While Hepatitis B viral load is considered one of the strongest predictors of HCC risk and can be managed with anti-viral medications, unfortunately, even in low-risk regions such as United States, roughly 3% of people currently living with chronic HBV are on treatment[14,21]. Several studies have shown the impact of socioeconomic status (SES) on health outcomes in cancer with populations of lower SES and less wealthy nations having significantly lower survival rates[32,59-61]. One retrospective analysis of European nations found nearly 20% variation in all-cancer relative survival between the least wealthy and most wealthy nations[61]. Similarly, low SES groups are associated with a variety of risk factors for poor outcomes in chronic HBV-related HCC. Despite 5-year survival rate for HCC in the United States increasing to 18% in 2019, the greatest benefits in survival and mortality are seen in groups with higher SES, while higher HCC incidence, later stage of diagnosis, and lower survival rates are seen in low-SES status groups[28,40]. Disadvantaged groups are typically minority ethnic groups such as African Americans and Hispanics as they tend to live in areas with the highest rates of family poverty, unemployment and high-school dropouts and thus may be associated with greater risk for HCC due to less access to screening and treatment[62].

Among patients with Medicaid insurance, the presence of comorbidities such as obesity, diabetes, alcohol, and tobacco use disorders combined with lower educational attainment contribute to liver disease such as alcoholic and NASH (ASH/NASH) and significantly overlap with liver disease from chronic HBV[63,64].

METHODS TO ADDRESS DISPARITIES

Targeted screening and prevention

Globally, chronic HBV and HCC cases are underdiagnosed. The 2016 Polaris Observatory study estimated that only 10% of infected people were diagnosed with HBV[51]. Chronic HBV infection is often asymptomatic and requires greater emphasis on screening, especially considering that HBV can

lead to HCC in patients without cirrhosis[13,42,65]. There is a geographic disparity in screening: About 2% of people with HBV knew their status in 2019 in Africa *vs* 22% in the Americas and 19% in the European region[21]. Additionally, there is likely underestimation of the true number of chronic HBV in the United States and other regions because high-risk populations have historically been under-represented in national surveys and surveillance studies, especially considering the large influx of yearly immigration to the US[24].

Early detection of tumors from screening in chronic HBV improves overall survival. A Randomized Controlled Trial study in Shanghai found that biannual screening in chronic HBV patients reduced HCC mortality by 37%[66]. An estimated 70% of liver cancer cases are preventable with risk factor modification and screening, thus judicious screening of high-risk populations with use of evidence-based guidelines can significantly reduce mortality from chronic HBV-related HCC[40]. The the American Association for the Study of Liver Diseases (AASLD) recommends HCC surveillance with ultrasound with or without AFP for all patients with diagnosed cirrhosis, and chronic HBV carriers who are high risk including African Americans older than 20 years, Asians older than 40 years, and those with family history of HCC. However, less than 1 in 5 high-risk patients are regularly screened[67]. Although greater than 90% of patients with acute HBV experience resolution of disease and the small minority develop chronic HBV infection, 40% of chronic HBV patients go on to develop cirrhosis, liver failure and HCC, and up to 25% of patients with chronic HBV end up dying from cirrhosis or HCC; thus HCC screening has been found cost-effective in patients with HBV even without cirrhosis when incidence of HCC is greater than 0.2% per year[67,68].

Health literacy

Lack of health literacy is particularly apparent in vulnerable and underserved populations such as immigrant populations, Mexican Americans, and African Americans, who already disproportionately bear the burden of chronic HBV and HCC[69,70]. Increasing social awareness of risk factors and protective factors of chronic HBV can be an avenue to improve health literacy. Social media is used by much of the developed world. For example, World Hepatitis Day is an annual health education campaign led by the WHO in July that heavily utilizes social media to make a call to action to bolster efforts in prevention, screening, treatment and to spread awareness of viral hepatitis[71]. Culturally sensitive approaches are necessary with an increasingly diverse population of the United States, to effectively communicate with various ethnic groups. One such example is "photo novels" developed to cater to specific cultures which have been shown to be effective in increasing HBV awareness and screening in underserved populations[72].

In many developing countries, such as those in Sub-Saharan Africa and the Asia-Pacific region where the majority of global chronic HBV and HCC cases occur, there is limited knowledge of hepatitis B and the benefits of the HBV vaccine[1,11,12,73]. Only two percent of the patients in African and Southeast Asian regions were aware of their chronic HBV status in 2019[1]. There is a dire need for informational campaigns in these endemic regions to increase awareness and health education amongst vulnerable populations in addition to the national immunization programs that must be initiated at the federal level with support from international health organizations.

CONCLUSION

Chronic HBV infection continues to have significant impact globally despite escalating vaccine coverage, screening techniques and availability of anti-viral medications. The close geographic relationship between endemic chronic HBV and increased burden of HCC remains to this day in Africa and the Asia-Pacific regions comprising the vast majority of HBV-related HCC in the world. HBV and HCC disproportionately affect certain ethnic groups within the United States and worldwide, many of which are of low SES. Men and the elderly are disproportionally affected at greater rates. To mitigate this largely preventable disease, enhanced access to screening, vaccinations, surveillance, and treatment must be achieved to reduce the burden of chronic HBV and HCC worldwide.

FOOTNOTES

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