Understanding the Changing Landscape of Health Disparities in Chronic Liver Diseases and Liver Cancer

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Abbreviations:
AANHPI Asian Americans, Native Hawaiians, and Pacific Islanders
AL Allostatic load
AC Alcohol-related cirrhosis
ALD Alcohol-related liver disease
AUD Alcohol use disorder
AI/AN American Indian/Alaska Native
BMI Body mass index
CLD Chronic Liver Disease
COVID-19 Coronavirus disease-2019
FADS fatty acids desaturase
HIV Human immunodeficiency virus
HAA heterocyclic aromatic amine
SDoH Social determinants of health
LC-PUFA long chain polyunsaturated fatty acid
MO Mexican-Origin
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MSM  Men who have sex with men
NAFLD Nonalcoholic fatty liver disease
NASH Nonalcoholic steatohepatitis
NHW Non-Hispanic White
PNPLA3 patatin-like phospholipase domain-containing protein 3
SES Socioeconomic status
SGM Sexual and gender minorities
T2D Type II diabetes

Abstract
Liver disease and liver cancer disparities in the U.S. are reflective of complex multiple determinants of health. This review describes the disproportionate burden of liver disease and liver cancer among racial, ethnic, sexual, and gender minority, rural, low socioeconomic status (SES) populations, and place-based contexts. The contributions of traditional and lifestyle-related risk factors (e.g., alcohol consumption, evitable toxin exposure, nutrition quality) and comorbid conditions (e.g., viral hepatitis, obesity, type II diabetes) to disparities is also explored. Biopsychosocial mechanisms defining the physiological consequences of inequities underlying these health disparities, including inflammation, allostatic load, genetics, epigenetics, and social epigenomics are described. Guided by the National Institute on Minority Health and Health Disparities (NIMHD) framework, integrative research of unexplored social and biological mechanisms of health disparities, appropriate methods and measures for early screening, diagnosis, assessment, and strategies for timely treatment and maintaining multidisciplinary care should be actively pursued. We review emerging research on adverse social determinants of liver health, such as structural racism, discrimination, stigma, SES, rising care-related costs, food insecurity, healthcare access, health literacy, and environmental exposures to pollutants. Limited research on protective factors of liver health is also described. Research from effective, multi-level, community-based interventions indicate a need for further intervention efforts that target both risk and protective factors to address health disparities. Policy-level impacts are also needed to reduce disparities. These insights are important, as the social contexts and inequities that influence determinants of liver disease/cancer have been worsened by the coronavirus disease-2019 pandemic and are forecasted to amplify disparities.

Keywords: liver disease, liver cancer, health disparities, social determinants, liver health
Chronic Liver Disease and Cancer Disparities

Introduction
Liver diseases and liver cancer, including hepatocellular carcinoma (HCC), are important public health concerns in the United States (US), reflected by their growing economic burden. Compared to historical trends, liver disease and liver cancer mortality in the past decade are high. Liver disease/cancer disproportionately impact certain racial and ethnic, low socioeconomic status (SES), and other populations that experience health disparities (see the National Institute on Minority Health and Health Disparities (NIMHD) website). In this review, we describe liver health disparities, detail risk factors, social contexts that contribute to these disparities and their pathways, describe interventions to reduce disparities, and discuss opportunities for future research. Understanding the complex and changing landscape of liver health disparities is critical to move the field forward to reduce the high rates of, and alleviate worse outcomes for, liver disease/cancer among populations experiencing health disparities. Moreover, the impact of the coronavirus disease-2019 (COVID-19) pandemic has further exacerbated health disparities and long-ranging implications for liver disease/cancer diagnosis and management.

Epidemiology of Liver Cancer and Liver Diseases
Racial, ethnic, sexual and gender minority populations and underserved rural and/or lower SES communities experience complex inequities across social, behavioral, and biological determinants of health, which influence disparities in liver disease incidence and progression to liver cancer. Chronic liver diseases (CLD) represent a broad spectrum of conditions of progressive liver function deterioration, and include chronic hepatitis B (HBV) and C (HCV) viral infections, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), liver cirrhosis, and liver cancer, among others. CLD has greater prevalence and mortality among all racial and ethnic minoritized and low SES populations. HBV and HCV are preventable contributors of CLD and HCC-related mortality for racial and ethnic minority populations. Increased alcohol-related liver disease (ALD) and alcohol-related cirrhosis (AC) prevalence has been greatest among populations experiencing health disparities, and constitute the highest adult inpatient costs compared to all non-alcohol-related diseases combined. Health disparities also exist in the prevalence of NAFLD and NASH, other principal causes of CLD and HCC. HCC is a rising cause of cancer-related deaths in the US with race and ethnicity-based incidence and survival disparities. We describe these racial, ethnic, gender, and geographic disparities in detail below.

Racial and Ethnic Disparities
While liver cancer general population outcomes have recently improved, there remain notable racial and ethnic disparities in incidence and mortality (see Figure 1). Compared to Non-Hispanic Whites (NHWs) (7.7 cases per 100,000), all other racial and ethnic populations have a higher burden of liver cancer that is increasing, with American Indian/Alaskan Native (AI/AN) persons having the highest incidence (21.2), followed by Hispanic/Latino (15.3), Asian Americans, Native Hawaiians, and Pacific Islanders (AANHPI) (12.5), and non-Hispanic Black
(10.8) populations\textsuperscript{17}. Liver cancer incidence has improved since 2007 among AANHPIs, historically at highest risk, yet this population continues to have elevated liver cancer risk\textsuperscript{17,18}. Mortality continues to increase for AI/AN populations, who have the highest rates (17.1%), compared to non-Hispanic Blacks (13.4%), Hispanics/Latinos (13.3%), AANHPIs (13.2%), and NHWs (8.4%)\textsuperscript{18}. Race and ethnicity-based disparities in HBV, HCV, NAFLD, NASH, AC, and overall cirrhosis in liver disease prevalence and severity also exist\textsuperscript{18,19}.

Chronic HBV and HCV can lead to CLD, cirrhosis, liver failure, and liver cancer\textsuperscript{20}. Chronic HBV disparities are significant, with most US infections in Asian Americans (58\%)\textsuperscript{20}. AANHPIs are at highest risk, over ten times more likely than NHWs, of infection. Foreign-born individuals, often from countries in Asia, the Pacific Islands, or Africa with medium to high HBV prevalence, account for 70\% of chronic HBV in the US\textsuperscript{20}. However, AI/ANs remain at highest risk for acute and chronic HCV, with over twice the risk of NHWs\textsuperscript{17,20}. Acute HCV has also increased substantially in women of reproductive age, with AI/AN women at highest risk for HCV, though they remain understudied and underrepresented in research\textsuperscript{21-23}. Finally, HCV-related mortality is highest in AI/AN and non-Hispanic Black populations\textsuperscript{20}. Generally, HBV and HCV-related mortality has decreased with treatment advances, though access to the continuum of care remains a challenge for racial and ethnic minority populations and socioeconomically disadvantaged communities\textsuperscript{24}.

NAFLD prevalence has more than doubled over the last few decades and fibrotic NASH prevalence is also high\textsuperscript{25}, with well-documented disparities in incidence and progression of liver diseases\textsuperscript{15,16}. For instance, 3.4\% of Mexican-Origin (MO) Hispanics/Latino US adults aged 18 and over self-reported the highest liver disease prevalence, followed by Hispanics/Latinos overall (2.7\%) and AI/ANs (2.5\%), with other racial and ethnic populations reporting lower rates\textsuperscript{19}. NAFLD disparities are alarming, with highest prevalence among MO Hispanics/Latinos (42.8\%), followed by NHWs (30.6\%), all Hispanics/Latinos (27.6\%), non-Hispanic Blacks (21.6\%), and Asian Americans (18.4\%)\textsuperscript{26,27}. Similarly, NASH prevalence is highest in Hispanics/Latinos (45.4\%), followed by NHWs (32.2\%), and is lowest in non-Hispanic Blacks (20.3\%)\textsuperscript{28}. However, CLD and cirrhosis mortality are twice as high (and rising) in AI/ANs versus Hispanics/Latinos\textsuperscript{20} (see Figure 2). When Native Hawaiian and Pacific Islander (NHPI) data is reported separately from Asian Americans, NHPI are over twice as likely of CLD mortality (7.9 versus 3.4 per 100,000)\textsuperscript{30}. AI/AN liver disparities have been attributed to alcohol abuse and HBV, yet newer evidence emphasizes HCV and NASH etiological influences\textsuperscript{31}.

In recent years, high-risk drinking, alcohol use disorder (AUD), and ALD prevalence have increased, with the largest increases occurring in populations that experience non-ALD disparities\textsuperscript{11}. ALD with significant fibrosis is also increasing, indicating potential treatment gaps and accelerated progression\textsuperscript{32}. ALD and AUD prevalence vary by race and ethnicity\textsuperscript{33}, and by subpopulation\textsuperscript{34}, with AI/AN populations experience the highest ALD mortality burden\textsuperscript{35}.

These data are likely an underrepresentation of liver disease/cancer burden of underserved populations and demonstrate racial and ethnic disparities in liver disease/cancer are complex, dynamic, and require early detection and effective treatment access.

**Overlap of Race, Ethnicity, Age, Sexual and Gender Based Disparities**

Overall, liver disease/cancer burden is highest among men\textsuperscript{18,30}, however, applying an intersectional lens and considering disparities based on overlapping race, ethnicity, age, and gender and sexual identities concurrently is critical to understanding and reducing liver health disparities\textsuperscript{36,37}. AI/AN men have double the liver cancer risk than women (Table 1), with incidence (3.9\%) and mortality (2.5\%) rising annually\textsuperscript{17,18}. In Hispanic/Latina women, steady
annual increase in liver cancer incidence (2.4%) and mortality (1.1%) from 2000-2019, despite stabilization in other populations, is a concerning trend that may lead to future disparities. Mortality has also been increasing (1.5% annually) for non-Hispanic Black women. NAFLD prevalence is higher among men, however, women are equally likely to develop NASH and have a higher risk of developing advanced fibrosis. In chronic hepatitis, estrogen in women may play a protective role protective role in slower fibrosis progression and later cirrhosis onset. However, sex-based metabolic differences may place women at higher risk for ALD incidence and mortality. Understanding the role of social context and behavior in gender-based etiological disparities is needed to address increasing liver disease risk and accelerated disease progression in women.

Although racial and ethnic minority population data is insufficiently powered to demonstrate earlier disease onset, there is evidence of earlier onset of risk factors in youth. Liver cancer incidence for boys/men aged under 20 years and girls/women of reproductive age (15-39) has increased since 2000. Increased HBV and HCV prevalence among women of childbearing age has also increased the risk for maternal-to-child transmission. Additionally, HBV/HCV disparities exist for sexual and gender minority (SGM) populations. Men who have sex with men (MSM) have an elevated risk for HBV/HCV, with HIV-positive MSM at substantially increased HCV risk.

Place-based and Geographic Disparities

Place-based health determinants in racial and ethnic populations influence liver disease and liver cancer risk. Trends by geographic regions further depict disparities in risk factors. Liver cancer trends in mostly Pacific and Southern States, such as those with highest incidence (e.g., Oregon, California, New Mexico, Texas, Louisiana, Hawaii, and the District of Columbia) also have large AI/AN, Hispanic/Latino, and non-Hispanic Black populations (see Figure 3). States with higher mortality rates (e.g., New Mexico, Texas, Louisiana, Mississippi) show similar patterns of a historical context of forced migration. States with higher incidence/mortality rates for individuals aged < 50 years, including Alaska, Kentucky, and New York (incidence) and Hawaii, Mississippi, Rhode Island, and the District of Columbia (mortality) reflect areas with higher concentrations of AI/AN and other racial and ethnic minority populations, higher incarceration rates of these populations, and greater opioid use prevalence. Texas, especially South Texas, has exceedingly high rates of liver disease/cancer. This has been attributed to the state’s large Hispanic/Latino population and unique ethnicity and nativity composition that is predominantly US-born (71%) and Mexican-Origin (MO) (87%). This geographically-based disparity represents a concentration of risk factors disproportionately experienced by this population, since individuals are more likely to be of lower SES and have little or no healthcare coverage. Recently, a 50% NAFLD
prevalence was reported among Arizona MO Hispanics/Latinos, who face similar place-based burdens as South Texas MO Hispanics/Latinos. Geographic variations in HCC incidence also reflect risk factor distribution, such as alcohol use, type II diabetes (T2D), and obesity, that vary by racial and ethnic population.

**Disease Risk Factors**

Several risk factors for liver disease/cancer are well-established in the literature. Population-level differences in these risk factors, including susceptibility to HBV/HCV infection, genetics, obesity and T2D, and health behaviors, can help to explain liver health disparities and illuminate potential points of intervention.

**Susceptibility to HBV/HCV**

Individuals from racial and ethnic minoritized, SGM, and low SES populations are more likely to experience risk factors for HBV/HCV and are less likely to have access to appropriate screening, prevention, and treatment. These populations are at greater risk for behaviors related to HBV/HCV infection and serious complication, such as experiencing unstable housing or homelessness, incarceration, drug use (injection or non-injection), and present/past CLD, T2D, or living with HIV/AIDS. Additionally, while overall rates of HBV vaccination in the US are low compared to global rates, racial and ethnic minority populations have the lowest vaccination rates and are especially vulnerable to infection and disease progression. Importantly, all marginalized populations at risk of health disparities with HBV/HCV or adverse liver health are often unaware and live with undiagnosed and untreated infections and liver damage for decades, developing cirrhosis, end-stage liver disease, or HCC.

**Lifestyle-Related Risk Factors**

**Alcohol.** Regular alcohol consumption increases liver cancer risk fivefold and is a causal factor in the development of ALD. Alcohol consumption and its consequences vary across populations and may also contribute to disparities. Limited by structural barriers to healthy coping behaviors, such as SES, individuals from racial and ethnic minority and/or lower SES backgrounds may cope with stressors through alcohol use, increasing risk of worse liver-related outcomes. Additionally, well-established substance use disorder risk factors, including low SES, trauma exposure, and posttraumatic stress disorder, are higher in AI/ANs and other racial/ethnic minority populations. Unique to AI/ANs, racial trauma and poor community health also contribute to AUD. Among SGM, increased vulnerability to AUD likely occurs through similar substance use disorder pathways. Women are also less likely to receive AUD treatment. Acknowledging population-based differences in the clinical course of AUD will aid in the development of culturally congruent prevention and treatment programs.

**Toxins.** Fungal toxins, aflatoxins and fumonisins are substances that contaminate corn, peanuts, wheat, soybeans, ground and tree nuts, rice and other crops that are also implicated in risk of liver disease/cancer. Among Hispanics/Latinos, greater exposure to these toxins occurs through higher consumption of corn products and disproportionate representation in agricultural and food processing occupations. Long-term exposure to aflatoxin may play a causative role in 4.6% to 28.2% of global liver cancer cases, and combined with HBV/HCV infection, increases liver cancer risk. In a study of mostly South Texas MO Hispanics/Latinos, HCV and aflatoxin were more likely present in those with liver cancer compared to controls. The convergence of
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environmental exposures and health behaviors in this population was reflected in their liver disease burden and cancer risk.

Nutrition. Diet and nutrition influence development and progression of liver disease/cancer, however few studies examine the role of diet in liver disease/cancer disparities. Nuanced associations among diet and eating behaviors related to race and ethnicity should be further explored, particularly in relation to diet quality. Diet quality is inversely related to NAFLD and other liver diseases across all race and ethnicities, however, racial and ethnic disparities exist based on likelihood of food insecurity, leading to poorer food quality, which are both tied to lower SES, and are independent risk factors for NAFLD.

Obesity and Type II Diabetes (T2D)

Obesity is a multifactorial condition and includes psychological, biological, and environmental components. Non-Hispanic Blacks (49.9%) and Hispanics/Latinos (45.6%) have the highest prevalence of obesity in the US, followed by NHWs (41.4%) and AANHPIS (16.1%). AI/ANs (15%) have the highest T2D prevalence, followed by non-Hispanic Blacks (12.1%), Hispanics/Latinos (11.8%), AANHPIS (9.5%) and NHWs (7.4%). NAFLD is associated with metabolic syndrome, obesity and T2D, and approximately one-third of individuals with obesity develop NAS. Additionally, obesity, metabolic disorder, and T2D are associated with a 2-to-3-fold increased risk of developing liver cancer. Increased NAFLD prevalence mirrors recent surges in T2D and obesity, especially among Hispanics/Latinos. Obesity and T2D are independently associated with education and income, such that having a college degree lowers obesity risk; less than a high school education or a family income below poverty level are linked to higher T2D risk. Advanced fibrosis in NAFLD is associated with higher body mass index (BMI)-defined obesity and is most common among Hispanics/Latinos. Higher central adiposity and visceral fat distribution related to NASH risk are observed in Asian American populations. Non-Hispanic Blacks and Hispanics/Latinos experience multifactorial influences that increase susceptibility to obesity and T2D development at younger ages. MO Hispanics/Latinos have higher obesity and T2D rates than other Hispanic/Latino populations, reflected in higher liver disease and cancer incidence, especially in South Texas. High NAFLD prevalence in the general population, along with a growing proportion of those with advanced fibrosis, is projected to further increase in relation to obesity and T2D and is expected to continue to disproportionately impact populations already experiencing obesity-related health disparities.

Biopsychosocial Pathways to Disparities of Risk Factors

Health disparities are physiological consequences of inequities based on race, ethnicity, sexual, and gender identity, rurality, and SES. The established biological pathways of the converging psychological and social determinants that impact health outcomes include inflammation, telomere lengths, allostatic load, genetics, epigenetics, and are growing as more physiological mechanisms of social burden are identified.

Inflammation. Linking adversity to disease, downregulated immunity and increased inflammation have been established among biomarkers of acute and chronic stress across the life course. Greater inflammation has also been observed in racial and ethnic minoritized populations. Additionally, lower personal and family SES have been associated with greater inflammation, and childhood SES has predicted inflammation in adults. Both ALD and
NAFLD\textsuperscript{99} etiology and progression are thought to be mediated by inflammatory pathways. Liver cancer is also associated with chronic inflammation arising from various etiologies, including HBV, HCV, ALD, and NAFLD\textsuperscript{100}. Significant liver inflammation has recently been reported in Asian patients with chronic HBV\textsuperscript{101}. Severe hepatic steatosis in Hispanics/Latinos was also positively associated with inflammation\textsuperscript{26}.

**Allostatic Load.** Allostatic load (AL) is a composite biomarker of the cumulative physiological burden of life events through indicators of biological functioning across a range of regulatory systems (e.g., blood pressure, obesity, cardiometabolic risk biomarkers, and inflammation)\textsuperscript{102}. The *weathering hypothesis* is a theoretical framework where AL is a physiological pathway underpinning health disparities and the chronic burden of social position across the lifespan\textsuperscript{103,104}. If AL is persistently high, as would be expected in populations experiencing health disparities, diseases occur. AL could link disparities in obesity, T2D, and NAFLD development, and explain the inflammatory response linked to adipose tissue expandability\textsuperscript{105}. AL has been used to investigate physiological consequences of social inequities, like systemic inflammation, to help explain health disparities between populations. Recent work has found non-Hispanic Blacks, MO and other Hispanics/Latinos had higher odds of having AL compared to NHWs, and AL was independently associated with T2D\textsuperscript{102}. Recommendations have also been made to consider AL in assessing NAFLD risk\textsuperscript{106}.

**Genetics.** Genetic and epigenetic factors influence susceptibility, progression, and recovery of liver diseases and liver cancer, and may help to explain some racial and ethnic disparities\textsuperscript{107}. Variability in patatin-like phospholipase domain-containing protein 3 (PNPLA3) across racial and ethnic populations has been especially significant in determining susceptibility to NAFLD and other liver diseases, with four-fold risk for individuals homozygous for the risk allele and an almost doubled risk among heterozygotes\textsuperscript{108}. PNPLA3 is predominantly expressed in liver and adipose tissue, is strongly associated with increased triglycerides in the hepatic content, increased lipogenesis, and is stimulated by glucose and insulin\textsuperscript{109,110}. The PNPLA3 risk allele is most prevalent in Hispanics/Latinos, with an estimated frequency of 59-77\% among MO Hispanics/Latinos\textsuperscript{111}. This contributes to the greater susceptibility of Hispanics/Latinos to NAFLD incidence and progression\textsuperscript{112}. PNPLA3 risk allele carriers are also predisposed to severe steatosis, greater susceptibility to NASH, fibrosis, and other liver diseases at lower BMIs, and earlier disease onset, with the strongest effects in Hispanics/Latinos\textsuperscript{113,114}. However, this influence varies by race and ethnicity, such that among risk allele carriers, non-Hispanic Blacks have lower CLD risk compared to Hispanics/Latinos, however non-Hispanic Black risk allele carriers have higher NAFLD and other CLD risk compared to non-carrier peers\textsuperscript{113,114}. Additionally, the fatty acids desaturase (FADS) gene locus, a haplotype that leads to lower biosynthesis of bioactive metabolites, such as long chain polyunsaturated fatty acids (LC-PUFAs), is prevalent in AI/AN populations, resulting in greater susceptibility to inflammatory states and conditions\textsuperscript{115}. Given the disproportionate burden of liver disease among AI/AN and MO individuals, FADS may also play a role in the inflammatory pathways that contribute to susceptibility and progression of liver disease in populations with greater indigenous American ancestry\textsuperscript{88,116}. Inherited autoimmune diseases (e.g., primary biliary cirrhosis), or metabolic conditions (e.g., hereditary hemochromatosis), also impact liver disease and liver cancer susceptibility and progression\textsuperscript{117}. Relating epigenetic changes\textsuperscript{104,118} and gene regulation measures
to social context and health risks and advantages promises to provide further insight into the variability of liver health outcomes and the nature of how multiple levels interact to influence liver health. However, little research has linked these mechanisms to liver disease/cancer, social determinants of health (SDoH), and ancestry.\textsuperscript{119,120}

**Social Determinants of Liver Outcomes**

Multiple overlapping factors acting at different levels—biological, behavioral, environmental, cultural, and societal—contribute to health disparities in the US. Liver disease/cancer disparities cannot be fully explained by established risk factors, as they are also shaped by systemic and structural barriers.\textsuperscript{18,88,90} SDoH are known to play key roles in driving health disparities broadly. In recent years, research has begun to examine the roles of SDoH in the context of liver disease/cancer disparities.

**NIMHD Research Framework**

The NIMHD Research Framework\textsuperscript{121} provides a guide for inquiry to effectively inform and address the reduction of liver disease and liver cancer health disparities. The NIMHD research framework is a multilevel, multidomain model that depicts a wide array of health determinants relevant to understanding and addressing minority health and health disparities and promoting health equity.\textsuperscript{121} Understanding and addressing health disparities in all of their complexity and promoting health equity requires applying a multidimensional research lens.\textsuperscript{121} The NIMHD research framework is a tool for conceptualizing and depicting the broad range of determinants that promote or worsen minority health and/or cause, sustain, or reduce health disparities. Conducting research entirely within one cell of the framework—such as examining biological or behavioral factors at the individual level to characterize the etiology of the liver disease—does not sufficiently address cumulative or interactive effects of multiple determinants.

The framework specifies that health outcomes can also span multiple levels (individual, family and organizational, community, and population), across domains of influence, and identifies the importance of a life-course perspective, including consideration of early adverse life events, chronic, cumulative environmental exposures, transgenerational transmission of risk and resilience, and critical or sensitive periods when exposures may have heightened impact on health outcomes. NIMHD encourages use of this framework by liver disease/cancer researchers, educators, and others to promote a multidomain, multilevel approach to health disparities research and in developing treatment and intervention approaches.

**Exposure to Multilevel Discrimination**

Health disparities represent systems of privilege with discrimination of various types and levels that exert deleterious impacts.\textsuperscript{58} Individual-level discrimination can include internalized views or discriminatory experiences. Interpersonal discrimination occurs in the context of social interactions and can range from micro-aggressions to criminal acts of hatred. Structural racism includes explicit and non-explicit rules, laws, and place-based or institutional norms that impact access to resources. Liver health disparities research requires acknowledgement of the influence of structural racism as a driver of health disparities, moving beyond interpersonal discrimination to systemic racism present in all institutions that sustain self-reinforcing, inequitable social structures.\textsuperscript{122} Persistent exposure to discrimination has been related to accelerated epigenetic aging.\textsuperscript{123} Moreover, stigma likely contributes to health behaviors that increase disease risk.\textsuperscript{124} Historic marginalization of AI/ANs, non-Hispanic Blacks, Hispanics/Latinos, Asian Americans,
and NHPIs have led to economic disparities, poor access to quality education, and increased challenges to public safety\textsuperscript{122}. The effects of structural racism and discrimination on disease risk throughout life, in the context of historical generation, on susceptibility and resistance to exposures, are wide-ranging and continue to be identified.

\textit{Socioeconomic Status}

Factors linked to individual and neighborhood level SES have received some investigation in liver disease/cancer disparity research. SES reflects historical legacy and social patterns of inequality that shape social position, access to resources, and often overlaps with belonging to a racial and/or ethnic minority, rural, SGM, and/or immigrant population. Poverty and low SES have been linked to poorer HCV outcomes at the individual level\textsuperscript{6}. Low SES is linked to higher HCC incidence and mortality\textsuperscript{125} and worse liver-related AUD\textsuperscript{35,69} outcomes in racial and ethnic minority populations.

Children from socioeconomically-deprived neighborhoods have earlier NAFLD onset\textsuperscript{126}. Among adults, local socioeconomic deprivation was associated with a 48\% increased risk of HCC incidence and 136\% increased risk of CLD mortality\textsuperscript{54}. Differences in alcohol outlet density and health behaviors, including cigarette smoking, alcohol consumption, and dietary intake, explained the largest proportion of the association between local deprivation and CLD mortality\textsuperscript{54}. In addition to greater susceptibility to liver diseases and cancer, individuals belonging to lower SES categories are also faced with the economic burden of affordable treatment and disease management. Healthcare spending in the US for patients with CLD or cirrhosis is substantial, has increased for decades, and is disproportionately directed toward acute management (i.e., increased hospitalizations, emergency department visits, readmissions), reflecting a need for greater emphasis on preventive efforts\textsuperscript{2}.

\textit{Food Insecurity}

Food insecurity, which is closely associated with SES and disproportionately affects populations that experience liver disease disparities, is also an independent risk factor for liver disease\textsuperscript{6}. Individuals with food insecurity have limited access to fresh fruits and vegetables and ample access to lower-cost, convenient foods related to increasing obesity risk\textsuperscript{91}. Food insecurity is related with elevated NAFLD and advanced fibrosis risk, even after adjusting for demographic, socioeconomic, and behavioral health characteristics\textsuperscript{79}. Food insecurity also creates challenges and worsens outcomes for NAFLD and cirrhosis patients recommended to adhere to a low-salt/high protein diet\textsuperscript{6}. COVID-19 pandemic-related challenges are likely to worsen racial and ethnic and SES-based disparities in food insecurity\textsuperscript{6}.

\textit{Healthcare Access and Health Literacy}

Inequities in healthcare access and literacy contribute to liver health disparities across the healthcare continuum, ranging from prevention to screening, and surveillance to treatment. The timely detection and appropriate treatment of liver disease/cancer is of concern among populations experiencing health disparities. Lack of health care access often results in late diagnosis, inadequate or limited access to treatment, and poor survival rates. Potential barriers to HBV screening, vaccination, and treatment include patients' lack of knowledge regarding HBV and its complications, limited English fluency, stigma, financial and institutional barriers, differences in cultural expectations, and a lack of understanding and utilization of healthcare systems, further diminishing motivation to seek care\textsuperscript{127,128}. Gaps in provider knowledge also
represent a significant barrier to screening, for instance, 43% of primary care providers practicing in an urban, safety-net hospital setting were unfamiliar with HBV guidelines. Access to direct-acting antiviral agents (DAAs) for timely HCV treatment is a crucial step to reducing disparities in viral hepatitis elimination efforts. Non-Hispanic Black (18%), Hispanic/Latino (13%), and Asian (27%) patients are less likely to be treated for chronic HCV than NHW patients; lower treatment rates in Hispanics/Latinos occurred despite highest cirrhosis rates. Individuals with Hispanic/Latino ethnicity or who are uninsured have the lowest treatment rates, although privately insured patients have over three times the treatment rate of those who are Medicaid-insured. Medicare and privately insured patients also initiate treatment sooner than Medicaid-insured patients. Medicaid’s lack of expansion and late-stage fibrosis, sobriety, and prescriber eligibility requirements are barriers to equitable DAA therapy access. Recipients residing in states with these restrictions who self-identify as other than White have lower treatment rates. Removal of treatment eligibility restrictions can help to eliminate race and ethnicity-based differences in Medicaid-insured treatment rates.

Documented racial disparities in treatment also include lower HCC screening and liver transplantation referral rates among Black patients. Appropriate surgical therapy for HCC was also significantly underused for non-Hispanic Black and Hispanic/Latino patients compared to NHW or Asian patients. Curative HCC therapy has also been used less frequently among Hispanic/Latino (36%) and non-Hispanic Black (33%) patients, compared to NHW patients. Importantly, Black-white disparities usually observed in HCC survival did not exist in studies conducted in academic settings, suggesting equitably accessible high-quality care drives these disparities. Likewise, race and ethnicity were not associated with HCC curative treatment receipt or survival after adjusting for health system and insurance status, also suggesting race and ethnicity-based HCC survival disparities are partially explained by equitable access to high quality healthcare.

Environmental Exposures

Environmental exposures can place individuals from marginalized populations at higher risk for liver disease. Early-life environmental exposures (e.g., pollution) may contribute to liver disease through effects on obesity and gestational T2D. Environmental exposures occurring more commonly in populations that experience disparities are associated with epigenetic changes related to increased susceptibility to liver disease and liver cancer. Contaminated groundwater, exposure to organic solvents, and occupational exposures have been shown to increase HCC risk and disproportionately impact at-risk populations.

The Impact of COVID-19 on Liver Health Disparities

The COVID-19 pandemic has amplified the consequences of social contexts and inequities on determinants of liver disease and liver cancer, particularly among racial and ethnic minority populations. The substantial collateral impact of the COVID-19 pandemic includes adverse economic effects, limited or delayed access to health care, more progressive disease among care-seeking patients, psychosocial strain, and increased alcohol use, with greater post-pandemic increases among racial and ethnic minority populations. ALD and NAFLD mortality have increased most sharply during the pandemic (2020-2021), with steeper increases among women for all CLD. AI/ANs experienced the largest increases in NAFLD and ALD mortality and the highest NAFLD mortality rates.
Data since the onset of the COVID-19 pandemic suggest that persons with pre-existing liver disease and/or liver cancer experience poorer outcomes from COVID-19 infection (e.g., liver failure, long COVID-19). Higher mortality is reported among CLD patients infected with COVID-19; HCC, decompensated cirrhosis, and ALD are independently associated with mortality risk. Thus, COVID-19 treatments are needed for patients with CLD, along with safety and efficacy testing of the COVID-19 vaccine and health communication strategies that promote awareness of this elevated risk among patients with CLD. To address disparities exacerbated by the collateral impact of the COVID-19 pandemic on SDoH, a concerted effort amongst researchers and health care providers conducting multi-level (individual, community, and societal levels) interventions that address, identify, and support social and behavioral protective factors and modify health behaviors that increase liver disease risk are needed.

**Protective Factors**

Most health disparities research has focused on understanding risk factors with limited attention to the role of protective factors. Heterogeneity of protective factors may differentially mitigate health disparities in liver disease and liver cancer in different populations. For example, coffee consumption varies by culture and may be protective against NAFLD and liver fibrosis. There is also evidence suggesting physical activity has a protective effect against liver diseases, likely in part due to its effects on fat storage and/or BMI. Increased physical activity, independent of body weight, improved hepatic inflammation among patients with NAFLD. Specifically, leisure-time aerobic physical activity and resistance training have been linked to reduced NAFLD risk. Given that individuals belonging to populations that experience health disparities often do not engage in recommended levels of physical activity due to structural, financial, environmental, or other barriers, it is important to consider implications of limited access to protective effects and their impacts on health behaviors and outcomes. For instance, a healthy microbiome may also protective against liver diseases, particularly NAFLD. Certain microbiota are associated with reduced NAFLD risk in obesity, even among children. A healthy microbiome is typically indicative of higher quality diet, adequate physical activity levels, and other indicators of healthy lifestyle that may be more difficult for marginalized populations to achieve.

**Interventions to Reduce Liver Disease and Liver Cancer Disparities**

As our understanding of risk and protective factors of liver disease and liver cancer disparities is refined, it is also important to not delay in developing interventions to reduce disparities through targeted implementation of appropriate behavior change and addressing barriers with cultural and practical sensitivity. Careful attention to the context in which these disparities occur is critical in ensuring the success of interventions. Most interventions to date have focused on prevention, screening, vaccination, and/or management of HBV/HCV. For example, various HBV interventions have been conducted to promote screening among Korean American, Vietnamese American, or Asian American populations more broadly. HCV interventions have focused on a variety of populations that experience HCV disparities, including screening in low-income, primarily Hispanic/Latino baby boomers, HCV treatment for adults experiencing homelessness, HCV screening and treatment for AI/ANs, training and support for primary care physicians to treat Black patients seeking HCV care, and HCV treatment in rural adults. Intervening on disease risk behaviors, such as needle exchange programs and/or opioid substitution therapy are also strategies for preventing HCV.
transmission in persons who inject drugs, although efficacy in HCV prevention requires further high-quality research.162

Community engagement is necessary to develop and implement sustainable and effective interventions, promote trust, and appropriately tailor efforts to communities’ shifting needs (i.e., language, culture, changing access to resources). Because SDoH are multilevel, intervening at multiple levels is also critical. Existing multilevel, community-based interventions for HBV and HCV can serve as models for liver disease and liver cancer interventions in populations that experience health disparities. For example, Ma and colleagues154 conducted a successful HBV screening intervention among Vietnamese Americans recruited in collaboration with community-based organizers. Multilevel barriers to screening were addressed through group education, patient navigation, community leadership, and engagement of healthcare providers. Another successful multilevel intervention focused on HCV screening and care in primary care practices serving low-income Hispanic/Latino communities156. Patients never screened for HCV were identified, screened, and linked to appropriate care.

Limited intervention research has focused on aspects of liver disease/cancer prevention beyond HBV/HCV; most have focused on increasing awareness of modifiable risk reduction behaviors. For example, a community-based liver cancer education intervention improved diet and reduced alcohol intake163 and increased liver cancer prevention knowledge164 among underserved Asian American, non-Hispanic Black, and Hispanic/Latino community members. Another liver cancer education program among healthcare providers and community organizations in the Cherokee Nation increased liver cancer risk awareness and prevention and the ability and intention to speak to a provider about liver cancer among community members152. Similarly, providers’ knowledge, awareness, ability to identify patients, and intention to speak to patients and recommend liver cancer screening improved165. These literacy and awareness interventions have potential impacts on disparate liver health outcomes, however interventions with direct impacts on clinical outcomes are also needed. Progress has been made in developing effective interventions for some aspects of liver cancer and liver disease disparities, but several unexplored potential points of intervention remain, particularly SDoH (see Figure 4). Policy-level interventions have increased treatment and eliminated race- and ethnicity-based HCV treatment disparities, indicating that higher level interventions are essential to advance liver health equity.24

Gaps, Opportunities, and Recommendations

While evidence ties SDoH to liver disease/cancer outcomes in populations experiencing health disparities, little is known about how social determinants interact with biological and behavioral risk and protective factors to influence disparities. For example, the field of social epigenomics has linked social experiences, including food insecurity, exposure to racism, violence, migration, psychosocial stress, and social inequality119, to epigenetic changes. The use of epigenetic aging, telomere length and other emerging measures of integrative social and biological pathways are also needed to fully understand disparities. Further research that seeks to address gaps in our understanding of the multilevel and multidomain factors that may contribute to health disparities in liver disease/cancer—including overlapping biological, environmental, lifestyle, psychological, social, and healthcare system factors—is critical to inform development of effective prevention and treatment strategies for at-risk populations.

Progress in the field requires studies examining interactions and making comparisons between multiple risk and protective factors and developing a better understanding of protective factors in health disparities. Certain SDoH also remain relatively unexplored across and within
populations that experience liver disease/cancer disparities, including interpersonal or structural racism and discrimination; place-based health outcomes of understudied geographic regions of the US; and healthcare access and utilization among populations with health disparities.

Research on heterogeneity in incidence, severity, and progression of liver disease must be conducted in understudied and underserved racial and ethnic minority populations and varied contexts to fully capture mechanisms driving disparities in liver health. There are some populations for which research SDoH related to liver disease is needed, including AI/AN, NHPI, and SGM populations. There is also a need for research of disaggregated racial and ethnic populations that have historically been treated as monoliths, such as Asian Americans.

Among populations with greater liver disease/cancer risk, more research on diagnostic tools for early detection is needed, including testing of appropriate screening methods. Although improved national surveillance and updated guidelines for HCV screening and testing have recently been developed for various populations (e.g., adolescents, adults, baby boomers)\textsuperscript{130,166}, recommendations and supporting resources for populations experiencing disparities still need to be developed. Culturally appropriate and multilingual programs with linkage to appropriate care are still needed to increase HBV screening and vaccination efforts. Fostering early screening, vaccination (including infants to reduce mother-to-child transmission)\textsuperscript{42}, diagnosis, assessment, and treatment strategies (e.g., serum biomarker tests, radiologic tests, transient elastography) while maintaining multidisciplinary care should be actively pursued. Improving access to HBV and HCV treatment among racial and ethnic minority and socioeconomically disadvantaged populations is critical to advancing equity in this area, as HBV/HCV are progressing undetected and untreated in at-risk populations\textsuperscript{128,130}. Policy-level changes and tailored interventions will be needed to facilitate behavior that supports liver health and prevents onset and progression of preventable and treatable causes of CLD and HCC, such as HBV and HCV, and AUD.

Overall, research on interventions to reduce health disparities in liver disease/cancer is limited outside of the context of HBV/HCV interventions. Multilevel, community-based interventions are able to address many interrelated components of disparities. However improving health behaviors (i.e., alcohol risk reduction), HBV vaccination uptake, and uptake of other appropriate healthcare measures, especially among AI/ANs and Hispanics/Latinos, is needed, given recent liver disease/cancer trends in these populations\textsuperscript{31,167}. Research is also needed for strategies to overcome barriers to closing liver disease/cancer gaps for at-risk, underserved communities. Systems-level interventions are most impactful and can potentially reduce significant equity barriers, such as insurance-related and other disparities linked to healthcare access\textsuperscript{134}. As research continues to clarify integrative mechanisms linking SDoH and liver disease/cancer, it will be important for the research community to turn its attention toward developing interventions and models of care that seek to reduce liver health disparities and promote liver health equity in all populations.

References

   https://doi.org/10.1002/hep4.1747


Chronic Liver Disease and Cancer Disparities


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https://doi.org/10.1007/s11606-014-3057-9


Chronic Liver Disease and Cancer Disparities


community-based liver cancer education initiative led to healthier dietary and alcohol use behaviors among racial/ethnic minority community members. In *Cancer Epidemiology, Biomarkers & Prevention* (Vol. 31, pp. PO-161): American Association for Cancer Research.


### Figure Legends

**Figure 1**: Trends in age-adjusted mortality rates for liver and intrahepatic bile duct cancer by race and ethnicity: United States, 2000–2019.


**Figure 2**: Age-adjusted mortality rates for chronic liver disease and cirrhosis by race and ethnicity, U.S., 2010–2018.


**Figure 3**: Age-adjusted incidence rates for liver and intrahepatic bile duct cancer by state, 2014–2018

Figure 4: Key messages
Table 1. Liver and intrahepatic bile duct age-adjusted mortality rates per 100,000 persons by race, ethnicity, and gender, 2015-2019

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<th>American Indian/ Alaskan Native</th>
<th>Hispanic/ Latino</th>
<th>African American/ Black</th>
<th>Asian American, Native Hawaiian, and Pacific Islander</th>
<th>All Races and Ethnicities</th>
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<tr>
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<td>13.2</td>
<td>13</td>
<td>12.8</td>
<td>9.7</td>
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Source: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov)
Liver diseases and liver cancer disproportionately impact racial, ethnic, and other marginalized populations

- Disparities occur in part due to population differences in traditional risk factors for liver disease and cancer, including viral hepatitis, genetic factors, obesity, & risk behaviors
- Only limited research has examined social determinants of liver health (e.g., culture, socioeconomic deprivation, systemic and interpersonal racism)

Interventions must target identified risk and protective factors with careful attention to culture and context to reduce disparities

- Most interventions addressing liver health disparities have focused on HBV/HCV awareness and screening
- Future interventions should address risk and protective factors, including multilevel, multidomain social determinants of health

The NIMHD Research Framework provides a model to guide future research

- Understanding and addressing liver health disparities in their complexity requires a multilevel, multidomain approach
- Integrative studies that account for interactions between multiple risk and protective factors are critical