


An Analysis of Individual and Contextual-Level Disparities in Screening, Treatment, and Outcomes for Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and affects patients of all genders, races, ethnicities, and socioeconomic status. While the causes of HCC are numerous, the primary etiology is cirrhosis from alcohol and non-alcoholic fatty liver disease in the United States and from infectious agents such as Hepatitis B and Hepatitis C in the developing world. In patients at-risk for developing HCC, screening is recommended with ultrasound imaging and alpha fetoprotein laboratory tests. In socio-economically vulnerable patients, however, individual-level barriers (eg, insurance status) and contextual-level disparities (eg, health facilities) may not be readily available, thus limiting screening. Additional challenges faced by racial/ethnic minorities can further challenge the spectrum of HCC care and lead to inadequate screening, delayed diagnosis, and unequal access to treatment. Efforts to improve these multilevel factors that lead to screening and treatment disparities are critical to overcoming challenges. Providing health insurance to those without access, improving societal challenges that confine patients to a lower socioeconomic status, and reducing challenges to seeking healthcare can decrease the morbidity and mortality of these patients. Additionally, engaging with communities and allowing them to collaborate in their own healthcare can also help to attenuate these inequities. Through collaborative multidisciplinary change, we can make progress in tackling disparities in vulnerable populations to achieve health equity

Keywords: hepatocellular carcinoma, healthcare disparities, social determinants of health

Background

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and affects people of all genders, races, ethnicities, and socioeconomic status.¹ Worldwide, the incidence varies from region to region, with the highest incidence in Asia and Africa where more than 20 people per 100,000 are diagnosed with HCC.¹ In the United States, the incidence is lower at about 5 per 100,000.² Worldwide, males are nearly twice as likely to develop HCC as females, and the median age of diagnosis is 62.^{3,4}

Patients with underlying liver disease are at particularly high-risk for developing HCC.² In the United States, the predominant cause of HCC is cirrhosis mainly from alcohol and non-alcoholic fatty-liver disease.⁵ In the developing world, however, infectious etiologies such as Hepatitis B and C are the principal causal agents.⁶ A patient's underlying genetic factors may also predispose the individual to develop HCC including alpha-1 antitrypsin deficiency.⁷ Additionally, having multiple risk

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factors may have a synergistic effect on the risk of HCC development. For example, patients with Hepatitis C and heavy alcohol intake have a 2.3 times greater odds of developing HCC than patients with Hepatitis C alone.⁸

The incidence of HCC increased throughout the world in the 1980s and 1990s as the incidence of Hepatitis C virus, diabetes, obesity, and metabolic syndrome has increased.¹ On the other hand, over the past decade, increased screening for at-risk patients, changes to the epidemiology of underlying liver disease (eg treatment for Hepatitis B and Hepatitis C), broadened surgical indications, and improved availability of systemic therapy, have led to a decrease in HCC incidence, prevalence, and mortality throughout the western world.^{9,10} However, despite these medical advancements, disparities in outcomes remain among vulnerable populations (eg, racial/ethnic minorities, low-income populations, uninsured) due to unequal distribution, access, and receipt of medical care.¹¹ As a result, significant disparities across the HCC continuum, from screening to treatment to outcomes, exist. Investigation into the causes of these disparities is warranted in an effort to ameliorate inequities and improve survival for all patients with HCC. The objective of this paper is to provide a contemporary review of individual-level (eg, race/ethnicity and insurance) and contextual-level [social determinants of health (SDoH)] measures that impact disparities in HCC screening, treatment, and survival outcomes.

Contextual-Level Measures

Social determinants of Health (SDoH) are contextual-factors, apart from medical care that influence healthcare outcomes (Figure 1). They encompass five general domains that categorize the challenges faced by vulnerable populations.^{12,13} These domains include: neighborhood and built environment, social and community context, health and healthcare, economic stability, and education.¹²

Neighborhood and Built Environment & Social and Community Context

Neighborhood-level income can influence the diagnostic rates (upstream effects) and outcomes (downstream effects) of patients with HCC.¹⁴ In fact, patients with the highest socioeconomic status, as defined by neighborhood-level income, were found to have a 10% increased survival advantage when compared to patients at the lowest income level.¹⁵ While some of these outcomes may be attributed to access-to-care and health insurance disparities, discussed later, additional factors must be explored to fully understand why these disparate outcomes by income are seen.¹⁶

Patients from low-income neighborhoods have a higher incidence of HCC than the general population.¹⁷ Increased risk factors may help to explain this phenomenon, and one explanation is that individuals living in these low-income neighborhoods may have challenges in affording nutritious and health food options or may experience food

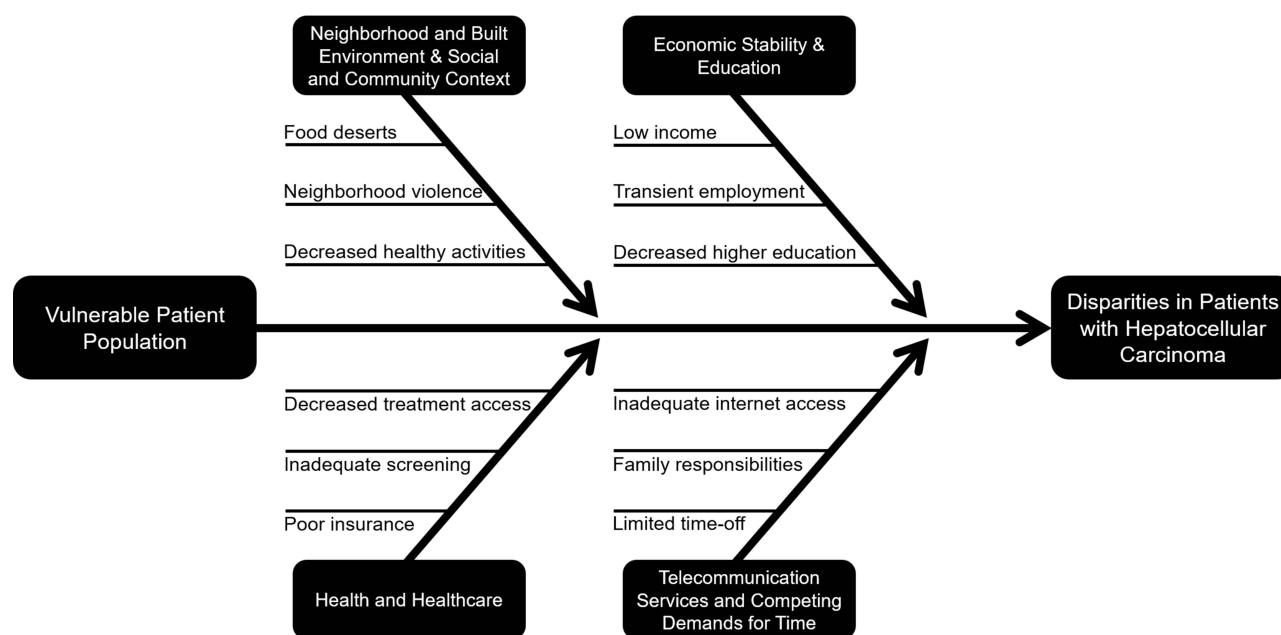


Figure 1 Contextual-Level Measures of HCC Disparities in Screening, Treatment, and Outcomes.

insecurity.^{18,19} These patients turn towards high-fat and carbohydrate rich foods from fast-food chains due to their lower cost.^{20,21} In addition to cost constraints, availability of fresh produce may be limited to patients of lower socioeconomic status due to food deserts in many of their communities.²² Studies have demonstrated that individuals in lower socioeconomic neighborhoods tend to live further from supermarkets than those in more affluent areas.²³ This high-fat, nutritionally poor diet may predispose patients to develop nonalcoholic fatty liver disease, a common cause of cirrhosis that can lead to the development of HCC.^{24,25}

Individuals from low-income neighborhoods also tend to have an increased prevalence of diabetes and obesity, coupled with decreased exercise due to lack of green space and parks, increases risk for non-alcoholic fatty liver disease associated-HCC that has been demonstrated in both human and mouse models.^{26–30} Additionally, low-income neighborhoods tend to have increased neighborhood violence, and individuals may be resistant to partake in outdoor activities.^{31,32} The cumulative effects of decreased exercise and increased diabetes can expedite HCC transformation in at-risk individuals and increase HCC tumor growth in patients who have already developed disease.^{27,33} While these factors may yield an increased incidence of HCC among individuals from low-income neighborhoods once a patient has a malignancy, early diagnosis and comprehensive treatment is necessary to improving outcomes.

Health and Healthcare

Access to health insurance can drastically alter the outcomes for patients with HCC.^{34–39} In patients with potentially curative (non-metastatic) disease, privately insured individuals have a median overall survival of 34 months, while patients without health insurance can have a median overall survival as low as 9 months.⁴⁰ Lack of health insurance has also been shown to be an independent predictor of decreased overall survival when controlling for other potential sociodemographic confounders.^{14,40} The exact etiology of this decreased survival in uninsured and underinsured patients is unknown, but numerous challenges faced by these patients may offer some understanding of the origins of this disparity.⁴¹

Patients without adequate health insurance coverage are less likely to be screened for HCC.^{42,43} These patients often lack a usual source of healthcare or primary care physician.⁴⁴ In patients who have annual well-care

physicals, as recommended by the Centers for Disease Control and Prevention, physicians may discover potential risk-factors or early signs of cirrhosis based on history, physical exam, or laboratory findings.^{45,46} In these patients with concerning features, additional laboratory and imaging tests can be ordered to uncover occult malignancies (eg HCC).⁴⁷ In high-risk patients where a malignancy is not discovered, a screening protocol can be implemented to identify HCC in its early stages.⁴⁸ These services may be inaccessible to patients without health insurance.

Screening is recommended for all patients with cirrhosis of the liver, regardless of etiology.⁴⁷ Patients are screened with ultrasound and serum alpha fetoprotein levels to uncover malignancies in the liver parenchyma.⁴⁹ Additionally, the 2018 guidelines by the American Association for the Study of Liver Disease recommend screening for patients at high risk for Hepatitis C including current or former intravenous drug users, patients who received solid organ transplantations, patients who received a blood transfusion before 1992, or those born between 1945 and 1965.^{48,50,51} Those with diagnosed Hepatitis C require close follow-up, and are screened with an abdominal ultrasound and alpha fetoprotein levels every six months if cirrhosis develops.^{50,52} Patients without insurance often are not able to obtain these screening services due to lack of access to a primary care physician to order screening exams.⁴¹

Early diagnosis of HCC, and most other malignancies, is imperative to improve clinical outcomes.⁵³ If identified early, HCC may be treated with local ablations or smaller curative operative interventions.⁵⁴ If diagnosed at later stages, however, multimodal treatment consisting of systemic therapy, liver-directed-therapy, extensive surgical resection, or even liver transplantation may be required.⁵⁵ Not surprisingly, studies have demonstrated that patients without insurance are more likely to be diagnosed with later-stage or metastatic disease than patients with adequate coverage.⁴³ This drastically affects survival outcomes and drives the disparity seen between insurance types.⁴⁰

Even if uninsured or underinsured patients are diagnosed with curative HCC, navigating the healthcare system remains a challenge. Studies have shown that access to cancer care coordinators or patient navigators can improve clinical outcomes.⁵⁶ These navigators are able to more easily schedule appointments with specialists, arrange for necessary imaging or procedures, and increase screening by up to 50%.^{57,58} Uninsured patients are often

without these patient navigators and have a more difficult experience in schedule these appointments.⁵⁸ This may cause patients to wait weeks to months to visit with all necessary specialists and can significantly delay care and lead to disease progression.⁵⁹

Frequent medical appointments with medical oncologists, surgical oncologists, radiation oncologists, and other medical specialties may also be challenging and costly due to transportation costs, time off work, and copayments for patients without insurance.⁶⁰ Additionally, many facilities do not offer systemic therapy, liver-directed therapies, or surgery for patients unable to cover the cost.⁶¹ Moreover, patients without health insurance face additional challenges in the postoperative period or while on systemic therapy such as frequent treatment visits and eventually surveillance visits.⁶⁰ While the first few visits are often covered with the cost of the surgery, subsequent follow-up visits require out-of-pocket expenses.⁶² Patients without health insurance therefore do not maintain consistent follow-up and should complications or symptoms of recurrence arise, they are not discovered until they have caused significant morbidity, leading to greater financial toxicity.^{11,63} Additionally, in the postoperative period, access to nutritional support services, physical therapy, home health, and other ancillary support mechanisms may be out of monetary reach for patients without insurance.⁶⁴ These support mechanisms, while not always necessary, have been shown to improve outcomes in HCC.⁶⁵ The cumulative financial burden of the aforementioned challenges may be an underlying cause of disparities in survival outcomes between HCC patients with and without health insurance.⁴⁰

Economic Stability and Education

Inconsistent or inadequate employment may also lead to HCC disparities. Studies reveal that individuals of lower socioeconomic status are likely to have children that are also of lower socioeconomic status, perpetuating the cycle of poverty in families.⁶⁶ An underlying cause of employment disparities begins with disparate education systems in low-income neighborhoods in which these individuals (and future generations) reside.⁶⁷ Patients of lower socioeconomic status are also less likely to attain a high-school diploma, receive a bachelor's degree, or have a graduate or advanced professional degree, further limiting employment opportunities.⁶⁸

These inequalities in education among individuals from low-income neighborhoods leads to challenges in securing

stable employment.⁶⁹ These individuals are less likely to have jobs or careers that provide health insurance and can lead to the many disparities discussed above.⁶⁹ Additionally, the education barriers faced by individuals of lower socioeconomic status lead to lower wages and a decreased ability to pay for HCC treatment.⁷⁰ Finally, decreased education may lead to disparities in healthcare literacy, and patients may have challenges in participating in their own care and informed healthcare decision making, further exacerbating disparities in HCC survival outcomes.⁷¹

Individual-Level Measures

Race and Ethnicity

In addition to the aforementioned contextual-level disparities, racial and ethnic minorities face additional challenges when seeking HCC care.⁷² In particular, Black and Hispanic HCC patients must overcome barriers throughout their workup, diagnosis, and treatment of HCC.^{73,74} Both populations are more likely to be diagnosed with HCC in the emergency department than an outpatient facility, likely indicating a reduced screening of these patients.¹¹ As previously discussed, patients not afforded primary care and screening services are also more likely to present with later-stage disease that may not be amenable to curative-intent treatment.¹⁷ Additionally, Black patients are less likely to receive a liver transplant, and studies have demonstrated that even in Black patients who receive treatment with a liver transplantation, survival is still less than patients of other races.^{75–77}

Language

Language barriers also play a role in the disparities experienced by racial and ethnic minorities.⁷⁸ For example, many Hispanic patients may not be fluent in English.⁷⁹ Other patients of different racial and ethnic backgrounds may also have limited fluency in English. This provides barriers to these patients in a variety of ways. Jobs that provide health insurance may be less attainable to individuals without English literacy.⁸⁰ Minority patients that are not fluent in English may also face employment discrimination limiting access to careers that include adequate income, health insurance, and other important benefits.⁸¹

Additionally, racial/ethnic minorities may be undocumented in the United States.⁸² This further complicates the possibility of receiving health insurance, and many patients may be limited to hospital-based plans or

Medicaid insurance for those who qualify.⁸³ Furthermore, a scarcity of resources for individuals and their families who have recently migrated to the United States can lead to challenges in learning English and securing health insurance benefits.^{84–86}

Competing Demands for Time and Telecommunication Services

Additional individual-level measures of disparity may include competing demands for time. Patients with steady employment and insurance may have more job flexibility allowing for time off.⁸⁷ On the other hand, patients without job security may fear that if time is requested off, they may be in jeopardy of losing their jobs.⁸⁸ Additional individual-level measures that may affect HCC patients are childcare or other caregiver responsibilities that may make it challenging for patients to attend appointments.^{89,90} This can lead to delays in diagnosis, which has profound survival implications.⁴⁵

A more contemporary individual-level factor causing disparities in HCC patients are inequality in telecommunication services among patients. The COVID-19 pandemic has elucidated the possibility of seeing a physician remotely for clinical evaluations and follow-up visits.⁹¹ While telemedicine can help reach patients who cannot visit a clinic, such as those in rural or those with competing demands for time, the patient must have the appropriate technology to facilitate a telehealth visit.⁹² Although seemingly ubiquitous, high-speed internet services may also not be accessible to all patients.⁹³ Additionally, some patients of lower socioeconomic status utilize local libraries or public hotspots for their Internet connectivity, a barrier not conducive to engaging in a telehealth visit.^{94,95}

Strategies to Overcome Individual and Contextual-Level Barriers to Care

Access to Insurance

Insurance appears to be the most important factor affecting the diagnosis (upstream effects), treatment, and survival (downstream effects) of patients with HCC.^{11,40,96} As previously mentioned, median overall survival differs dramatically between patients with private health insurance (greater than 30 months) and those without any health insurance (less than 10 months).⁴⁰ Efforts must be made to increase health insurance accessibility and enrollment

for all HCC patients to improve screening and treatment delivery.⁴³ The Affordable Care Act has sought to expand access to all, and while many improvements have been made, much work is still needed in this arena.⁹⁷

Medicaid expansion is one way to continue to improve access.⁹⁸ Studies have revealed that access to Medicaid or any type of insurance can improve HCC screening.^{11,43} This suggests that having insurance, particularly plans that cover liver-directed therapies or surgical interventions, independently provide survival benefits to patients.^{40,99,100} In other malignancies, studies have shown that expansion of public health-insurance options has resulted in a lower percentage of late-stage diagnoses and ultimately improved survival.¹⁰¹

Enhanced primary care physician visits and screening services for insured patients may also lead to improved patient outcomes due to earlier diagnoses.⁴³ Additionally, patient navigators are often accessible to insured patients, which can help them to navigate the healthcare system and schedule appropriate appointments.⁵⁷ Finally, access to systemic therapy, liver-directed-therapies and surgical interventions are more accessible to patients with insurance.⁶¹ Given the importance of insurance across the HCC continuum, access to insurance remains a critical step in decreasing HCC disparities in vulnerable populations.

Improved Education Systems

While healthcare reform through access to care for all would be the “golden ticket” to health equity, addressing the root causes of healthcare disparities is also critical. As previously discussed, education can have profound impacts on future careers and access to insurance, along with other socioeconomic benefits.^{67,102} Investments must be made to improve school systems nationwide, ensuring all students have an equal opportunity for success.¹⁰³ An additional strategy to improve the education of individuals might be through the implementation of School Choice programs where parents can send their students to a school system with higher quality education.^{104,105} With better education, improved employment can be secured, and health insurance can be attained.¹⁰⁶

While the effects of poor school systems on future healthcare have previously been discussed, the effect of lost learning from the COVID-19 pandemic are not yet understood.¹⁰⁷ Students in many areas throughout the country and world were out of the classroom for many months to a year due to safety concerns from the COVID-

19 pandemic.^{107,108} Numerous studies predict lasting future effects on knowledge and performance on standardized examinations.¹⁰⁷ These effects are predicted to affect individuals of poor socioeconomic status more than affluent students.¹⁰⁹ This disparity may be due to more affluent children having tutors to fill learning gaps or parents that can remain home to work with them on their work.¹⁰⁹ Additional vigilance is necessary to make up for this lost knowledge, especially in low-income neighborhoods with individuals of poor socioeconomic status.¹¹⁰ Without careful attention, it is possible that future disparities in HCC and other cancer care will be exacerbated due to lasting effects of the COVID-19 pandemic.

Access to Healthcare

In addition to increased insurance access, efforts should be made to improve the ease in which a patient can access the healthcare system. Telehealth is growing in popularity throughout the world and has been particularly helpful throughout the COVID-19 pandemic.⁹¹ Although imaging and procedures cannot take place remotely, initial consultations, follow-up visits, and postoperative visits may be conducted through a virtual platform.¹¹¹ This expansion to telehealth services has improved the reach of providers, allowing for them to care for patients who may otherwise have difficulty accessing the medical system.¹¹² Additionally, patients who have competing demands for time, as discussed above, can consult with a physician without needing to leave their homes.⁹¹ There are, however, significant disparities that have been elucidated as telehealth has grown in popularity.¹¹²

As previously discussed, vulnerable patients may not have access to computers or high-speed internet services needed to facilitate a telehealth visit.¹¹³ Strategies must be implemented to bridge the technology gap among populations of different socioeconomic status. One strategy has been to provide broadband internet coverage to vulnerable communities.¹¹⁴ Additional initiatives have hoped to provide internet-ready devices that will allow for these telehealth visits.¹¹⁵ While technology can certainly ease the burden of frequent clinic visits, patients without access to these devices are subjected to continued disparities.¹¹²

In addition to telehealth and infrastructure challenges faced by many patients, others face challenges in securing transportation to their clinical appointments. In urban settings, many patients may not have vehicles and rely on public transportation to get to and from their medical appointments.¹¹⁶ After medical and surgical treatments

for HCC, many patients have significant physical challenges that make public busses and trains a challenging means of transportation.¹¹⁷ In fact, many patients are unable to follow-up due to inadequate transportation, and these missed appointments can negatively impact the trajectory of their HCC care.¹¹⁶ Programs to provide transportation can drastically improve attendance to clinic appointments and other scheduled visits.¹¹⁸ Some hospital-systems are providing these services to assist patients, but additional resources are available through Medicare and other insurance plans.¹¹⁹ Specifically, the Veterans Affairs healthcare system has a robust infrastructure to assist with transportation.¹²⁰ Of course, patients without insurance may not be afforded these opportunities, so local, regional, and national efforts should be made to improve transportation services to and from required medical visits.¹¹⁶

Culturally Competent Care and Community Engagement

As previously discussed, racial and ethnic minority patients are subjected to significant healthcare disparities.⁷² These disparities are exacerbated by disparate oncology care for malignancies such as HCC.¹²¹ Ensuring adequate access and equitable care for minority patients begins with understanding a patient's cultural beliefs and practices.¹²² For example, some cultures may have different approaches to cancer care with some patients choosing to keep their malignancy hidden from their families.¹²³ Other cultures may choose to involve many family members in healthcare decisions and treatment course.¹²³ Understanding these differences may help providers better care for patients and may help patients become more comfortable with their physicians.¹²⁴ One strategy to enhance patient comfort is to increase the hiring of diverse healthcare workers.¹²⁵ Racial and ethnic minorities are underrepresented in healthcare fields, but improved diversity may assist with patient comfort and trust as they can be cared for by a provider that understands their unique cultural considerations.^{126–128}

Translator and language services are also imperative to decreasing disparities in care for HCC and other malignancies.¹²⁹ While many patients are partially fluent in English, it is important to engage with an official interpreter or translator service when discussing important medical decisions, especially care for their HCC malignancy.^{129,130} Although providers may partially be fluent in a patient's native language, stylistic nuances

and different dialects that vary across country of origin can complicate patient and provider understanding.¹³¹

In addition to culturally competent care, disparities can be alleviated with enhanced community engagement for racial and ethnic minorities.¹²⁴ Patients in underserved communities appreciate engaging with healthcare providers so their healthcare needs can be understood.¹³² In some communities, patients may be interested in screening programs for malignancies, while other communities may have other concerns such as smoking cessation or sexually transmitted infections.^{132,133} Providers and healthcare systems must engage with community leaders to understand the needs of a particular community.¹³⁴ While these important considerations do not directly impact HCC care, gaining the trust of a community is a necessary first step to providing care. Finally, Federally Qualified Health Centers (FQHCs) offer patients a medical home where primary care and specialty services can be accessed within a community and may further assist in ensuring patient trust and improving health outcomes.^{135,136} Without trust between providers and individuals, patients may be wary of seeking screening services, consulting with a physician after diagnosis, or undergoing liver-directed therapies and surgical procedures for HCC.¹³⁷

Conclusions

HCC is a complex malignancy that requires comprehensive screening of at-risk patients and multimodality treatment regimens including systemic therapy, liver-directed therapy, and surgery. Individual and contextual-level measures can drastically impact the services accessible and treatments provided to patients with HCC. Providers and healthcare systems must continue to work towards providing equitable care to all patients in an effort to reduce disparities and improve healthcare outcomes in vulnerable populations.

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Disclosure

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