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Racial/Ethnic Disparities in Hepatocellular Carcinoma Epidemiology

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Abstract
Purpose of Review The current review aims to provide an updated analysis on race/ethnicity-specific disparities in hepatocellular carcinoma (HCC) epidemiology in the USA with a focus on HCC incidence and prevalence, HCC stage at diagnosis, HCC treatment received, and overall HCC survival.
Recent Findings While the overall incidence of HCC in the USA has stabilized, race/ethnicity-specific disparities persist. HCC incidence remains the highest among Asians, but the burden of HCC among Hispanics is rising and may reflect the significant burden of nonalcoholic fatty liver disease (NAFLD)-related HCC among this group. Furthermore, disparate implementation of HCC screening and surveillance, which detrimentally affects ethnic minorities and underserved populations to the greatest extent, contributes to lower rates of potentially curative therapies and lower overall survival among these groups, especially African Americans with HCC.
Summary Despite improvements in clinical care of HCC patients, persistent race/ethnicity-specific disparities in HCC outcomes persist and reflect multifactorial barriers. Highlighting these disparities is the first step towards raising awareness to guide future education and research to improve HCC outcomes for all groups.

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Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related mortality among men and sixth among women worldwide [1]. In the USA, HCC is the fifth and ninth most common cause of cancer-related deaths among men and women, respectively [2, 3]. Despite advances in HCC screening and surveillance, overall 5-year survival among HCC patients in the USA remains less than 30% [4]. The cause of low survival among HCC patients is multifactorial and reflects challenges in implementing consistent HCC screening and surveillance among high-risk populations resulting in advanced stage disease at presentation as well as limitations in treatment options with surgery being the primary curative option [5].

Despite the poor survival outcomes overall, several studies have demonstrated that HCC incidence in the USA has stabilized [3, 6•]. This likely reflects improved management of HCC risk factors, such as effective antiviral therapies for chronic hepatitis C virus (HCV) and chronic hepatitis B virus (HBV) infections. Other HCC risk factors such as nonalcoholic steatohepatitis (NASH) and alcoholic liver disease (ALD) have remained stable or increased. Racial/ethnic disparities in HCC incidence and survival outcomes are well reported and likely reflect race/ethnicity-specific differences in prevalence of HCC risk factors [6•, 7–10]. In addition, observed race/ethnicity-specific differences in HCC epidemiology may also reflect suboptimal awareness of HCC risk factors or implementation of HCC screening and surveillance among certain groups or underlying genetic differences that affect

disease progression and response to therapies [11, 12, 13••, 14]. The current review aims to provide an updated analysis of racial/ethnic disparities in HCC epidemiology with a focus on disparities in HCC diagnosis, HCC treatment, and HCC survival outcomes in the USA.

Racial/Ethnic Disparities in Hepatocellular Carcinoma Incidence and Prevalence

Between 2003 and 2011, a retrospective observational study using the Surveillance, Epidemiology, and End-Results (SEER) registry identified a total of 51,741 patients with HCC, with the majority of patients being non-Hispanic whites ($n = 26{,}759$), followed by Hispanics ($n = 8998$), Asians ($n = 8493$), and African Americans ($n = 6473$). However, the rising incidence of HCC disproportionately affected racial minorities, where Hispanics had the greatest increase in the incidence rate of HCC (+35.8%) between 2003 and 2011, whereas a decline in HCC incidence in Asians was observed [6•]. El-Serag and Kanwal reported similar findings with the greatest proportional increase in age-adjusted HCC incidence rate observed among Hispanics, followed by African Americans, non-Hispanic whites, and Asians [15]. Altekruse et al. noted similar epidemiological trends, where the greatest incidence rate of HCC was seen in African Americans, Hispanics, followed by non-Hispanic whites, compared to decreasing HCC incidence (−1.6%) in Asians [16]. Using data from SEER and the Texas Cancer Registry from 1995 to 2010, Ramirez et al. compared the HCC incidence among Latinos in Texas compared to non-Hispanic whites both within Texas and across other SEER regions in the USA. While the authors demonstrated that Latino males and females had HCC incidence three to four times higher than non-Hispanic whites, certain comorbidities including concurrent obesity and diabetes, which may not only increase risk of nonalcoholic fatty liver disease but also HCC itself could not be evaluated in detail [17]. While race/ethnicity-specific disparities in HCC incidence may be reflective of different disease etiologies and variations in underlying genetic risk factors, they may also reflect socioeconomic disparities that often run in parallel with race. Shebl et al. used SEER data to evaluate the association between measures of socioeconomic status and HCC risk [18]. The investigators demonstrated that within race/ethnic groups, patients with HCC had lower measures of socioeconomic status, particularly for Asians. Furthermore, immigrant status, which can also be associated with low socioeconomic status, was associated with higher HCC risk. Thus, while the study demonstrated that low socioeconomic status even within a race/ethnic group seems to increase HCC risk, it is difficult to sort out the interplay between race/ethnicity and socioeconomics as it relates to HCC risk.

Variability in the incidence of HCC between race/ethnic groups may arise from the race/ethnicity-specific distribution of HCC risk factors. The predominant risk factors for HCC include infection from chronic viral hepatitis (HBV or HCV), ALD, and nonalcoholic fatty liver disease (NAFLD) [3, 19, 20]. Although these risk factors are well-known for causing HCC, the impact of each is dependent on its prevalence in the general population. Welzel et al. utilized data from the SEER-Medicare registry from 1997 to 2007 to evaluate population attributable fractions (PAF) of risk factors for HCC in the USA [21]. In doing so, the authors attempted to better characterize the impact of specific HCC risk factors by evaluating both exposure to outcome associations along with the prevalence of each exposure in the population. It was noted that the presence of diabetes and obesity had the greatest impact on HCC risk among non-Hispanic whites (PAF of 39.8%) and Hispanics (PAF of 38.1%), whereas chronic HCV infection had the greatest impact on HCC risk among Asians (PAF of 35.3%) and African Americans (PAF of 34.9%) [21]. Alcohol-related disease had the second greatest impact on HCC risk among non-Hispanic whites (PAF of 25.6%), Hispanics (PAF of 30.1%), and African Americans (PAF of 18.5%). For Asians, chronic HBV infection had the second greatest impact on HCC risk (PAF of 28.5%) [21]. Makarova-Rusher et al. performed an updated analyses of PAF of HCC risk factors using the 2000–2011 SEER-Medicare database [22•]. Similar to the aforementioned study, metabolic disorders carried the greatest PAF HCC risk among all patients. Specifically, metabolic disorders carried the greatest HCC PAF risk among Hispanics and non-Hispanic whites, whereas chronic HCV infection contributed the largest PAF among African Americans and Asians. Thus, while race/ethnicity-specific differences in HCC reflect differences in underlying liver disease etiology, it is also important to recognize and treat other potential HCC risk factors (e.g., diabetes, obesity, metabolic syndrome) that also affect an individual's overall HCC risk.

While the majority of HCC in Asians worldwide is secondary to chronic HBV, the majority of HCC in the USA is secondary to cirrhosis from chronic HCV, ALD, and NAFLD. A recent study by Younossi et al. evaluated 2004–2009 data from the SEER-Medicare-linked registry and demonstrated that chronic HCV accounted for nearly 55% of all HCC in the USA; however, NAFLD-related HCC prevalence rose significantly during the study period, increasing by approximately 10% annually [20]. Race/ethnicity-specific disparities in the risk of metabolic syndrome may contribute to further racial disparities in the risk of NAFLD-related HCC [23, 24]. Although metabolic syndrome is comprised of many components, diabetes mellitus or glucose intolerance plays an important role in the risk of HCC. A recent meta-analysis observed that patients with diabetes mellitus had a 2.3-fold increased risk of developing HCC compared to non-diabetics [25]. Similar findings were reported in a prospective long-term

multiethnic cohort study assessing risk factors for HCC. The investigators noted that concurrent diabetes was associated with increased risk of HCC and this increased risk was seen among all race groups, with the greatest risk seen among Hispanics (RR 3.36, 95% CI 2.41–4.70) [26].

Racial/Ethnic Disparities in HCC Screening and Surveillance

Disparities in HCC awareness among both providers and patients can contribute to differences in timely access to HCC screening and surveillance among high-risk groups [13••, 14, 27•]. Delays in appropriate implementation of HCC screening and surveillance further contribute to delays in diagnosis, leading to more advanced disease at presentation, limiting potentially curative treatment options, and lower overall survival [12, 28–31]. Several studies have demonstrated low rates of HCC surveillance utilization in the USA and have also reported disparities in surveillance by race/ethnicity [29, 32•, 33]. Using the SEER-Medicare database, Davila et al. evaluated the use and determinants of pre-diagnosis HCC surveillance among patients with HCC who had a prior diagnosis of cirrhosis. Race/ethnicity-specific disparities in HCC surveillance were seen with the highest surveillance rates among Asian patients (28.1%) and the lowest rates among African American patients (12.2%) ($p < 0.001$) [34•]. Similarly, another study using the national Veterans Affairs (VA) registry examined the determinants of HCC surveillance among HCV-infected patients with cirrhosis and observed that African Americans were significantly less likely to receive surveillance compared to non-Hispanic whites (OR 0.60, 95% CI 0.45–0.81) [32•]. Another study by Singal et al. evaluated predictors of HCC surveillance among patients with cirrhosis at a large urban safety net hospital from 2008 to 2011. Among 904 cirrhotic patients, 67% of patient underwent inconsistent HCC surveillance, which was defined as at least one screening ultrasound performed during the 3-year period but not receiving annual or biannual HCC surveillance. The study noted that failure to recognize cirrhosis on the part of the providers was a significant barrier to implementing consistent HCC surveillance. Among the underserved population, race/ethnicity-specific disparities were also observed, where African Americans were significantly less likely to undergo consistent HCC surveillance compared to non-Hispanic whites (OR 0.61, 95% CI 0.42–0.99) [29].

While the exact etiology behind these race/ethnicity-specific disparities in appropriate HCC screening and surveillance are unclear, it has been suggested that both patient and provider awareness with HCC screening and surveillance guidelines may contribute. For example, Khalili et al. evaluated provider-reported screening practices for HBV and HCC screening, along with provider knowledge, attitudes, and perceived barriers to HCC screening among Asian Americans by surveying a large network of providers within San Francisco's safety net system [11]. Respondents reported suboptimal rates of HCC screening and noted that the most common perceived barriers influencing a provider's decision to perform HCC screening among HBV patients were lack of imaging resources (59%), unclear HCC screening guidelines (35%), difficulty accessing specialty care (35%), and patient financial barriers (31%) [11]. Similarly, a retrospective study by Sarkar et al. investigated predictors and patterns of HCC screening among HBV-infected Asian Americans. Among 824 patients at risk for HCC, screening (defined as ≥1 imaging and/or AFP per year) decreased from 67 to 47 to 24% from the first to the second to the tenth year after HBV diagnosis, respectively. Older age, female gender, presence of cirrhosis, prior testing for HBeAg, and more recent HBV diagnosis were all positively associated with receipt of appropriate HCC screening. Patients who were seen by gastroenterologists or hepatologists were more likely to receive regular HCC screening compared to internists or family practitioners, which suggests that provider knowledge and awareness may play an important role in screening [28]. Singal et al. performed a systematic review of the literature from January 1990 to March 2011 to evaluate overall utilization of HCC screening and surveillance among US adults with cirrhosis. While the overall rates of HCC surveillance among cirrhosis patients was only 18.4%, the investigators noted that patients followed in subspecialty gastroenterology clinics had significantly higher rates of HCC surveillance (51.7 vs. 16.9%, $p < 0.001$) [13••]. Dalton-Fitsgerald et al. further attempted to understand practice patterns and potential barriers to implementing HCC surveillance among primary care providers using a web-based survey of 131 providers [14]. The leading barriers to HCC surveillance included suboptimal knowledge of recommended HCC surveillance guidelines, difficulties in communicating effectively with patients about the importance of HCC surveillance, and having more important medical issues to manage.

Racial/Ethnic Disparities in Stage of HCC at Diagnosis

The stage of disease at diagnosis for HCC patients is not only a reflection of whether or not patients are appropriately linked to care and receiving HCC screening and surveillance, but ultimately affects treatment options and overall survival. For example, patients diagnosed with small solitary HCC may be eligible for curative approach with radio-frequency ablation or surgical resection, and patients with HCC diagnosed within the Milan criteria may be eligible for MELD exception points to improve priority for liver transplantation. Thus, race/ethnicity-specific disparities in HCC stage at diagnosis

are important to highlight as they may contribute to differences in treatment and overall HCC survival.

Within the USA, approximately 40% of all patients with HCC are diagnosed with localized disease at time of presentation [35]. When stratified by race/ethnicity, significant disparities in the stage of HCC at time of diagnosis have been observed. A recent retrospective cohort study using 2003–2011 SEER registry data reported that African Americans were 20% more likely to present with advanced stage HCC compared to non-Hispanic whites (OR 1.20, 95% CI 1.10–1.30, p value <0.001), whereas Asians were 13% less likely to present with advanced disease (OR 0.87, 95% CI 0.80–0.94, p value <0.001) [7]. Using two additional databases, the University Health Consortium and the Nationwide Inpatient Sample, Abbas et al. evaluated trends in the prevalence of metastatic HCC diagnoses from 2000 to 2011. The study demonstrated that lack of long-term insurance coverage and African American race/ethnicity were both independently associated with higher risk of metastatic HCC at presentation [36]. Although the exact reasons for race/ethnicity-specific disparities in stage of HCC at diagnosis are unclear, disparate implementation of HCC screening and surveillance may account for some of these differences. For instance, improvements in HCC screening and surveillance efforts among patients with chronic HBV, who are predominantly Asian in the USA, contribute to earlier detection of HCC among this population [28]. In addition, patient-specific factors such as complex psychological or social factors may also contribute to barriers in access and linkage to care, and these factors may impact ethnic minorities to a greater degree. Furthermore, attitudes and trust in the medical system may vary across populations, and distrust of medical care may limit the success of implementing HCC surveillance among at-risk patients. For example Schwei et al. evaluated a convenience sample of 569 adults in Chicago to assess their institutional trust of the health-care system based on sociodemographic factors and previous interactions with the health-care system. The study demonstrated that race/ethnicity was a strong predictor of institutional trust, with African Americans (OR 1.90, 95% CI 1.13–3.17) and Mexican-Hispanics (OR 2.34 95% CI 1.43–3.81) demonstrating significantly less trust in the health-care system compared to non-Hispanic white respondents [37]. Patterns of distrust in the medical community and suboptimal implementation of HCC screening and surveillance among at-risk patients may be particularly detrimental to underserved racial minorities. In addition, it is possible that tumor-specific differences may also contribute to variations in natural history of disease presentation. Underlying differences in tumor biology have the potential to affect HCC stage of disease at presentation, response to therapy, and long-term survival [38, 39].

Racial/Ethnic Disparities in Hepatocellular Carcinoma Treatment

Receipt of treatment among HCC patients is affected by multiple factors, including stage of disease at diagnosis and access to treatment options. Given that success and availability of curative options for HCC, including local tumor destruction, surgical resection, and liver transplantation, are affected by tumor burden, disparities in screening thereby affect disparities in the receipt of HCC treatment. Since the implementation of the MELD exception policy for HCC patients, greater allocation of potential curative therapies was observed among all patients with HCC compared to the pre-MELD era [7, 40–42]. Despite significant improvement with receiving HCC treatment in the post-MELD era, race/ethnicity-specific disparities in the receipt of treatment remain. A recent study by Ha et al. used the 2003–2011 SEER registry data and the United Network for Organ Sharing Organ Procurement and Transplantation Network (UNOS/OPTN) database to evaluate race/ethnicity-specific disparities in receipt of HCC treatment in the USA [7]. Among adults with HCC in the USA, the study observed that Hispanics (OR 0.76, 95% CI 0.67–0.77, $p<0.001$) and African Americans (OR 0.69, 95% CI 0.61–0.77, $p<0.001$) were significantly less likely to receive any treatment for HCC compared to non-Hispanic whites with HCC, whereas Asians were nearly 40% more likely to receive any treatment (OR 1.39, 95% CI 1.26–1.53, $p<0.001$) [7]. Similarly, when evaluating probability of receiving surgical resection or liver transplantation, Hispanics and African Americans were less likely to receive these therapies whereas Asians were more likely to receive these therapies. However, when specifically evaluating the trends in receipt of liver transplantation among adults with HCC, African Americans, Hispanics, and Asians were significantly less likely to undergo liver transplantation compared to non-Hispanic whites, and this disparity was observed in both the pre-MELD and post-MELD eras [10]. Additional studies utilizing different HCC cohorts reported similar findings with African Americans experiencing the lowest predictive probability of receiving any surgical intervention (i.e., tumor ablation, resection, and transplantation) for the treatment of HCC [42, 43]. As previously alluded to, cultural beliefs and distrust in the medical system may not only delay seeking health care but also influence the likelihood of receiving potentially curative therapy. In a retrospective cohort study of SEER data from 1984 to 2004, Wang et al. evaluated trends and impact of refusing cancer-directed surgery among adults with HCC. While the overall rates of refusal of cancer-directed surgery were low at 3.2% among eligible patients, older patients and African Americans were more likely to refuse treatment. As

expected, the study demonstrated that patients who refused therapy had significantly higher HCC mortality than those who accepted recommended therapy (HR 2.5, 95% CI 2.046–3.013, $p < 0.001$) [44].

Racial/Ethnic Disparities in Hepatocellular Carcinoma Survival Outcomes

HCC survival outcomes are directly affected by the cascade of clinical care beginning from HCC screening and surveillance for early detection to access and availability of HCC-directed treatment. While it is clear that race/ethnicity-specific disparities exist with respect to HCC diagnosis, stage of disease at presentation, and receipt of HCC treatment, it is equally important to understand the impact of these disparities on overall HCC survival outcomes.

By using data from the SEER registry, Altekruse et al. characterized trends in HCC mortality in the USA. From 2000 to 2010, HCC mortality rates significantly increased among non-Hispanic whites, Hispanics, and African Americans, whereas mortality rates decreased among Asians/Pacific Islanders [16]. It has been hypothesized that the decreased mortality among Asians with HCC may have resulted from greater awareness of HBV and greater awareness and implementation of HCC screening and surveillance programs among patients with chronic HBV, many of whom are Asians. Similarly, using SEER data from 1998 to 2010, Wong et al. evaluated the impact of MELD exception policy implementation on long-term survival among HCC patients and demonstrated significantly improved overall survival for HCC patients in the post-MELD era compared with the pre-MELD era. However, persistent race/ethnic-specific disparities in overall HCC survival were noted, where African Americans continued to have the worst overall survival in both the pre-MELD and post-MELD eras [41].

A recent study using updated SEER data from 2003 to 2011 again confirmed the race/ethnicity-specific disparities in HCC survival observed, with Asians demonstrating the highest crude overall 5-year survival, followed by non-Hispanic whites, Hispanics, and African Americans. These racial disparities persisted even after adjusting for stage of disease at diagnosis and treatment received [6•]. Similarly Njei et al. reported that African Americans with HCC had the worst overall survival and were independently associated with increased risk of mortality compared to other races (HR 1.24, 95% CI 1.13–1.36, $p < 0.001$) [45•]. These findings along with other studies continue to raise concern about race/ethnicity-specific disparities in HCC survival [9, 40, 46]. A possible rationale for these race/ethnicity-specific differences in survival may relate to differences in disease etiology and disease progression. The survival advantage among Asians could partially be explained by a lower prevalence of cirrhosis among HCC patients, given that chronic HBV is the predominant etiology of HCC in this population, and up to 20% of patients with HBV-related HCC are non-cirrhotic and thereby may have less severe hepatic dysfunction, thus more likely to be eligible for curative surgical therapies like primary resection. For example, Kao et al. compared prognosis between patients with HBV- and HCV-related HCC undergoing surgical resection and demonstrated that patients with HBV-related HCC had greater overall survival and lower incidence of HCC recurrence after surgical therapy [47]. These observations were attributed to significantly lower hepatic inflammation and better-preserved hepatic synthetic function among patients with HBV-HCC [47]. Other risk factors and comorbidities might also affect survival across racial groups, including alcoholic liver disease, diabetes mellitus, central obesity, and NAFLD. In addition, socioeconomic inequalities such as income, education, and employment; access to quality health care; and distrust in the health-care system may contribute to race/ethnicity-specific disparities in survival [6•, 40, 46, 48]. For instance, Artinyan et al. evaluated survival differences by income among HCC patients using the SEER and UNOS/OPTN data and observed that lower income HCC patients had worse survival when compared to the middle-income and high-income HCC patients [46].

Furthermore, using data from the 2011 Nationwide Inpatient Sample, Rajbhandari et al. evaluated racial disparities in in-hospital treatment and outcomes for HCC in the USA. Among a total of 22,933 HCC-related hospitalizations, non-Hispanic whites comprised the majority of HCC-related hospitalizations at 55% followed by Hispanics (16%), African Americans (16%), and Asians or Pacific islanders (8%). African American patients were found to be admitted less often for invasive HCC-related procedures, such as transplantation, resection, and ablation, despite presenting for medical care in an inpatient setting and having no significant differences in systemic or liver-specific comorbidities or metastatic disease at presentation [49]. In addition, racial/ethnic disparities in inpatient mortality rates were seen, where African Americans had significantly higher inpatient mortality compared to non-Hispanic whites (OR 1.58, 95% CI 1.12–2.24, $p = 0.009$) [49]. Even in the inpatient setting, which reduces the differences owing to access to care, race/ethnic disparities in HCC outcomes persists. The study suggests that the reasons for these racial/ethnic disparities are likely multifactorial, including health-care providers and patient-related factors, specifically, patient acceptance of invasive procedures, reduced quality of outpatient care, and barriers to care such as geographical (e.g., public transportation hassles), financial, and educational barriers.

In contrast to previous SEER studies, Aparo et al. analyzed HCC survival using data from a large academic medical center in Bronx, New York, and demonstrated that Hispanics experienced similar overall survival when compared to non-

Hispanic whites and African Americans [50]. However, in the SEER registry, Hispanics are mostly of Mexican descent, whereas Hispanics in the Bronx mostly originate from Puerto Rico or the Dominican Republic, and these differences in the subcategory of Hispanic groups may account for the differences observed. Race/ethnic disparities in socioeconomic factors such as education, income, and insurance status were less evident in the Bronx population compared to that of the SEER registry, suggesting that socioeconomic factors may have played a more significant role in the SEER registry patients.

Conclusions

In summary, race/ethnicity-specific disparities in HCC epidemiology persist with significant differences observed in incidence and prevalence, timely implementation of HCC screening and surveillance programs thereby affecting stage of disease at diagnosis, HCC treatment received, and overall HCC survival. While the exact etiology underlying these disparities is not clear, the current literature suggest that multiple factors including disease-specific (e.g., etiology of underlying liver disease), patient-specific (e.g., concurrent risk factors such as alcohol or attitudes towards medical care), provider-specific (e.g., provider knowledge and implementation of appropriate HCC screening and surveillance), and system-specific factors (e.g., disparities in access and linkage to care) all contribute to these disparities. Improved awareness of these disparities will help guide future research and targeted interventions to help improve overall HCC outcomes across all groups.

Compliance with Ethical Standards

Conflict of Interest John Ha, Melissa Yan, and Robert J. Wong each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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