

# Disparities in Hepatocellular Carcinoma Incidence, Stage, and Survival: A Large Population-Based Study

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## ABSTRACT

**Background:** Liver cancer is one of the most rapidly increasing cancers in the United States, and hepatocellular carcinoma (HCC) is its most common form. Disease burden and risk factors differ by sex and race/ethnicity, but a comprehensive analysis of disparities by socioeconomic status (SES) is lacking. We examined the relative impact of race/ethnicity, sex, and SES on HCC incidence, stage, and survival.

**Methods:** We used Surveillance, Epidemiology, and End Results (SEER) 18 data to identify histologically confirmed cases of HCC diagnosed between January 1, 2000 and December 31, 2015. We calculated age-adjusted HCC incidence, stage at diagnosis (local, regional, distant, unstaged), and 5-year survival, by race/ethnicity, SES and sex, using SEER\*Stat version 8.3.5.

**Results:** We identified 45,789 cases of HCC. Incidence was highest among low-SES Asian/Pacific Islanders (API; 12.1) and

lowest in high-SES Whites (3.2). Incidence was significantly higher among those with low-SES compared with high-SES for each racial/ethnic group ( $P < 0.001$ ), except American Indian/Alaska Natives (AI/AN). High-SES API had the highest percentage of HCC diagnosed at the local stage. Of all race/ethnicities, Blacks had the highest proportion of distant stage disease in the low- and high-SES groups. Survival was greater in all high-SES racial/ethnic groups compared with low-SES ( $P < 0.001$ ), except among AI/ANs. Black, low-SES males had the lowest 5-year survival.

**Conclusions:** With few exceptions, HCC incidence, distant stage at diagnosis, and poor survival were highest among the low-SES groups for all race/ethnicities in this national sample.

**Impact:** HCC prevention and control efforts should target low SES populations, in addition to specific racial/ethnic groups.

## Introduction

Despite a decline in overall cancer incidence and mortality rates during recent decades, liver cancer is one of the most rapidly increasing cancer types in the United States (1). The incidence of liver cancer has more than tripled since 1980, growing at approximately 3% per year from 2006 to 2015 (1, 2). An estimated 42,000 new cases of liver cancer were diagnosed in the United States during 2019 (1), and approximately 75% to 90% will be hepatocellular carcinoma (HCC), the most common form of primary liver cancer (1, 3).

The burden of HCC varies significantly by age, sex, and race/ethnicity. Incidence rates are two to three times greater among individuals over 55 years of age (4), and liver cancer is three times more common in males than females (2). Several studies report substantial differences in the incidence of, and mortality from, HCC by race/ethnicity in the United States (3, 5–7). Results from the 2003 to 2005 Surveillance, Epidemiology, and End Results (SEER) cancer registries indicate that HCC incidence rates were over three times greater among non-Hispanic Asians/Pacific Islanders (API) than among non-Hispanic Whites (Whites) (3). Other groups, such as non-Hispanic American Indian/Alaska Native (AI/AN), non-Hispanic Blacks (Blacks), and Hispanics/Latinos (Latinos), had HCC incidence rates that were lower than among API, but greater than among Whites, during this same period. However, the most recently available data from 2016 show that Latinos have the highest incidence of, and mortality from, liver cancer, followed by APIs, AI/ANs, Blacks (had a higher mortality than AI/AN), and Whites (4).

The primary risk factors for HCC include infection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV), heavy alcohol consumption, and obesity/metabolic syndrome, which are associated with nonalcoholic fatty liver disease (NAFLD) (8). The distribution of these risk factors in the United States has evolved over time and varies considerably by age, sex, and race/ethnicity. For example, chronic HBV infection rates are approximately 18 times higher in APIs compared with Whites (9). AI/ANs have the highest rates of both HCV infection and binge drinking, followed by Whites (9, 10). In addition, changes in the demographic landscape (e.g., the rapidly growing Latino population) and recent trends in the prevalence of risk factors in specific groups (e.g., high rates of obesity and diabetes among Blacks and Latinos) are important contributors to the increasing HCC incidence, mortality, and disparities observed in the United States.

Although HCC disease burden and risk factors are well-documented and observed to be greater in specific groups, few studies

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**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

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Cancer Epidemiol Biomarkers Prev 2021;30:1193–9

doi: 10.1158/1055-9965.EPI-20-1088

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have examined the association between race/ethnicity and socioeconomic status (SES) on HCC incidence and survival (11–14). Most of these studies examined the separate influence of race/ethnicity, SES, and sex on these two indicators, and none focused on stage at diagnosis as an outcome or included AI/ANs, despite their high-risk of HCC. Thus, we aimed to determine the differences in HCC incidence, stage, and survival, stratified by race/ethnicity, SES, and sex in a nationally representative sample.

## Materials and Methods

### Data source and study sample

Data for this study were obtained from the SEER 18 Registries (henceforth referred to as SEER 18), which include 18 population-based cancer registries in 14 states and cover 27.8% of the U.S. population (15). Data are available from these registries for cancer cases diagnosed from 2000 to 2015. We queried the SEER 18 Registries for invasive HCC cases that were diagnosed at age 20 or older and were histologically confirmed with ICD-O-3 (International Classification of Diseases for Oncology, Third edition) codes 8170–8175.

### Measures

We categorized the HCC cases into five mutually exclusive racial/ethnic groups: American Indian/Alaska Native (AI/AN), Asian or Pacific Islander (API), Black, Latino, and White. We used the SEER Historic Stage A variable, which is available from 2000 to 2015, to group the tumor stage at diagnosis into four categories: localized, regional, distant, and unstaged. Regional disease refers to cases with direct extension of the tumor beyond one lobe by contiguous growth and/or regional lymph nodes involved. Distant disease was diagnosed only when a distant site and/or node was involved.

We used census tract-level SES as a proxy for the patient-level SES. Census tract level-SES is a NCI defined variable, which we obtained from the SEER specialized database. A composite SES score for each census tract is obtained each year through a factor analysis of seven variables estimated by the U.S. Decennial Census survey and American Community Survey. These variables are: median household income, median house value, median rent, percent below 150% of poverty line, education index, percent working class, and percent unemployed (16). Census tracts are categorized into SES tertiles based on the composite SES scores across the entire catchment area. For our study, SES was classified as low, medium, or high based on the defined SES tertiles.

### Statistical analysis

We used SEER\*Stat version 8.3.5 to calculate the age-adjusted (to the 2000 U.S. standard population) incidence rate (per 100,000) of HCC and the respective 95% confidence interval by sex, race/ethnicity, and SES tertiles from 2000 to 2015. We then compared the incidence rate in the high-SES group to that in the low-SES group for each race/ethnicity group and sex using the Tiwari et al, 2006 modification provided by SEER\*Stat (17).

We calculated the proportions of cases diagnosed at the localized, regional, distant stage, as well as the unstaged cases by sex, race/ethnicity, and SES. The Chi-square test was used to compare stage at diagnosis distributions between the low-SES and high-SES groups, by race/ethnicity and sex. We also calculated the 5-year survival rate by race/ethnicity, sex, and SES using the Kaplan–Meier method and compared survival distributions among SES tertiles by race/ethnicity and sex using the Log-rank test. In addition, we used a multivariable Cox proportional hazards regression model to examine the relationship between SES and survival in patients with HCC adjusting for age, sex,

year of diagnosis, race/ethnicity, stage, and surgery of primary site. We performed statistical analyses using SEER\*Stat version 8.3.5 and SAS version 9.4, and considered *P* values less than 0.05 statistically significant.

## Results

We excluded cases without racial/ethnic information ( $n = 194$ ) or census tract-level socioeconomic data ( $n = 1,438$ ). For the survival analysis, we also excluded cases who were only reported through death certificate or autopsy and cases who were alive with no survival time ( $n = 752$ ).

### Sample characteristics

We identified 45,789 histologically confirmed HCC cases (Table 1). Overall incidence was 4.9 and mortality was 3.8 per 100,000 person-years. Whites comprised half of the analytic samples (52% incidence sample and 50% survival sample). AI/ANs made-up 1% of both samples, with the remaining portion composed of APIs (18% incidence sample, 19% survival sample), Black (12% incidence sample, 17% survival sample), and Latinos (18% incidence sample, 17% survival sample). A greater proportion of individuals in both samples were in the low-SES group than in the high-SES group (incidence sample: low-SES 35% vs. high-SES 31%; survival sample: low-SES 36% vs. high-SES 30%). The highest percentage of low-SES individuals (62%) and the lowest percentage of high-SES individuals (12%) was observed among Blacks, whereas the lowest percentage of low-SES individuals (23%) and the highest percentage of high-SES individuals (12%) was found among APIs. A similar racial/ethnic distribution was observed for the incidence/stage at diagnosis sample and the survival sample (Table 1).

### Incidence by race/ethnicity, SES, and sex

Figure 1 presents the age-adjusted incidence rate (per 100,000) for all HCC cases ( $n = 45,789$ ) by race/ethnicity and SES. Within each racial/ethnic group except for AI/ANs, SES gradients were observed for age-adjusted incidence rates, with lower SES groups having higher incidence rates than other SES groups. Incidence was highest among low-SES APIs (12.1) and lowest among high-SES Whites (3.2). Significant differences in incidence rates between high-SES and low-SES groups were observed among Whites, Blacks, APIs, and Latinos ( $P < 0.001$ ; Fig. 1). Overall, males had higher incidence rates than females and similar race/ethnicity-SES gradients were observed for both sexes (Supplementary Figs. S1A and S1B).

### Stage at diagnosis by race/ethnicity, SES, and sex

Table 2 presents the stage at diagnosis for all HCC cases by race/ethnicity and SES. High-SES APIs had the highest percentage of HCC cases diagnosed at the local stage (55%) of any racial/ethnic group, whereas high-SES AI/AN had the lowest (33%). Among AI/ANs, APIs, and Whites the proportion of cases diagnosed at a distant stage differed significantly when comparing the low-SES to high-SES groups ( $P$  values  $< 0.01$ ). No significant differences were observed in cancer stage distribution between the low-SES and high-SES groups for Blacks or Latinos. Medium-SES AI/AN had the highest percentage of distant stage disease (22%; 95% CI, 15.4%–28.5%), and high-SES AI/AN had the lowest (4.7%; 95% CI, 0%–9.9%). Among APIs, the proportion of cases diagnosed at a distant stage ranged from 13.1% (95% CI, 11.9%–14.2%) among those with high-SES to 18.4% (95% CI, 16.6%–20.1%) among those with low-SES. Among Whites, the proportion ranged from 16.4% (15.6%–17.2%) for those with high-SES to 18.6% (17.7%–19.6%) for those with low-SES. There is significant variation in the proportion of cases diagnosed at the distant stage by race/ethnicity

**Table 1.** Characteristics of the hepatocellular carcinoma cases, 2000 to 2015 [*n* (%)].

	Incidence/stage sample			Survival sample		
	Total	Females	Males	Total	Females	Males
<b>American Indian/Alaska Native</b>	431 (1)	132 (1)	299 (1)	377 (1)	120 (1)	257 (1)
Low SES	212 (49)	67 (51)	145 (49)	185 (49)	61 (51)	124 (48)
Medium SES	155 (36)	46 (35)	109 (36)	138 (37)	41 (34)	97 (38)
High SES	64 (15)	19 (14)	45 (15)	54 (15)	18 (15)	36 (14)
<b>Asian/Pacific Islander</b>	8,036 (18)	2,105 (19)	5,931 (17)	7,169 (19)	1,808 (20)	5,361 (18)
Low SES	1,874 (23)	487 (23)	1,387 (23)	1,681 (23)	424 (23)	1,257 (23)
Medium SES	2,771 (35)	716 (34)	2,055 (35)	2,480 (35)	624 (35)	1,856 (35)
High SES	3,391 (42)	902 (43)	2,489 (42)	3,008 (42)	760 (42)	2,248 (42)
<b>Black</b>	5,498 (12)	1,285 (12)	4,213 (12)	4,710 (12)	1,082 (12)	3,628 (12)
Low SES	3,407 (62)	837 (65)	2,570 (61)	2,917 (62)	696 (64)	2,221 (61)
Medium SES	1,406 (26)	303 (24)	1,103 (26)	1,208 (26)	262 (24)	946 (26)
High SES	685 (12)	145 (11)	540 (13)	585 (12)	124 (12)	461 (13)
<b>Hispanic/Latino</b>	8,134 (18)	2,045 (19)	6,089 (17)	7,171 (19)	1,743 (19)	5,428 (18)
Low SES	4,007 (49)	1,013 (50)	2,994 (49)	3,580 (50)	863 (50)	2,717 (50)
Medium SES	2,692 (33)	681 (33)	2,011 (33)	2,357 (33)	585 (33)	1,772 (33)
High SES	1,435 (18)	351 (17)	1,084 (18)	1,234 (17)	295 (17)	939 (17)
<b>Non-Hispanic White</b>	23,690 (52)	5,329 (49)	18,361 (53)	19,323 (50)	4,186 (47)	15,137 (51)
Low SES	6,484 (27)	1,514 (28)	4,970 (27)	5,429 (28)	1,221 (29)	4,208 (28)
Medium SES	8,754 (37)	1,907 (36)	6,847 (37)	7,153 (37)	1,486 (36)	5,667 (37)
High SES	8,452 (36)	1,908 (36)	6,544 (36)	6,741 (35)	1,479 (35)	5,262 (35)

(chi-square  $P < 0.05$ ). The proportion was highest in Blacks (20%) and lowest among APIs (15.6%;  $P < 0.001$ ; **Table 2**). Among males, similar differences in stage at diagnosis by SES were also observed for AI/ANs, APIs, and Whites, but not for Blacks or Latinos (Supplementary Table S1). No significant differences in stage at diagnosis were observed for females by SES in all racial/ethnic groups (Supplementary Table S2). However, with few exceptions, females were more likely to be diagnosed at the local stage and less likely to be diagnosed at a distant stage than males (Supplementary Tables S1 and S2).

**Five-year survival by race/ethnicity, SES, and sex**

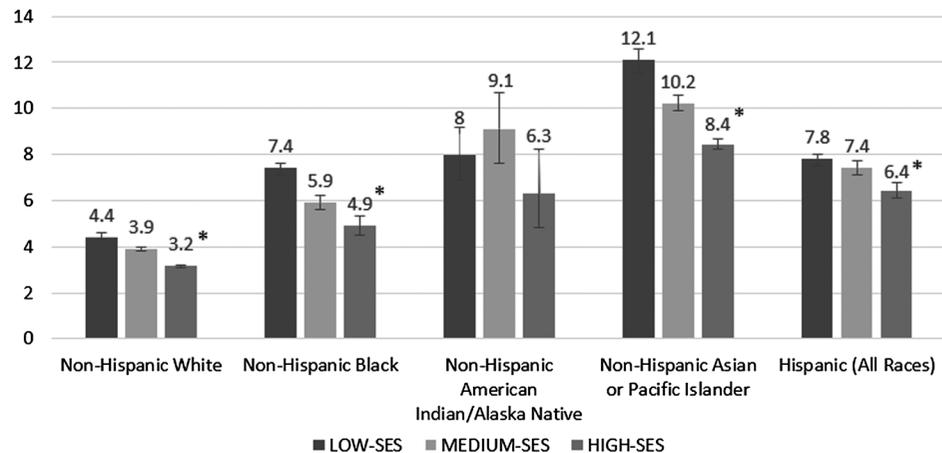
**Figure 2** presents a comparison of 5-year survival for all HCC cases ( $n = 38,750$ ) by race/ethnicity and SES from 2000 to 2015. Five-year survival was highest among high-SES APIs (30.0%; 95% CI, 28.2%–31.9%) and lowest among low-SES Blacks (11.5%; 95% CI, 10.2%–12.9%). Significant survival differences were observed by SES among all racial/ethnic groups (log-rank  $P$  values  $< 0.001$ ), except AI/ANs. However, survival was virtually identical for high-SES (20.3%; 95% CI, 17.9%–23.0%) and mid-SES Latinos (19.2%; 95% CI, 17.5%–21.2%).

We also examined survival rates by SES and race/ethnicity for males and females. Among males, we found significant survival differences by SES in all racial/ethnic groups (log-rank  $P$  values  $< 0.001$ ), except AI/ANs. Five-year survival was highest among high-SES APIs (31.0%; 95% CI, 28.8%–33.1%) and lowest among low-SES Blacks (9.7%; 95% CI, 8.4%–11.2%; Supplementary Fig. S2A). Among females, significant differences in survival by SES were observed among Blacks (log-rank  $P = 0.01$ ) and Whites (log-rank  $P < 0.01$ ), in which survival was significantly longer among high-SES and medium-SES females than low-SES females. Five-year survival was greatest among high-SES API females (27.3%; 95% CI, 23.9%–30.9%) and lowest among high-SES AI/AN females (10.5%; 95% CI, 3.0%–23.7%; Supplementary Fig. S2B).

In addition, we examined the relationship between race/ethnicity, SES, other covariates, and 5-year survival among HCC cases after adjusting by age, sex, year of diagnosis, stage at diagnosis, and surgery of primary site. Our findings indicate that significant survival differences between Blacks and Whites persist even after adjusting for stage and surgery (Supplementary Table S3).

**Figure 1.**

Age-adjusted incidence rate (per 100,000) for all HCC cases ( $n = 45,789$ ) by race/ethnicity and SES from 2000 to 2015. \*, indicates a statistically significant difference in incidence rate comparing High-SES group to the Low-SES group ( $P < 0.05$ ).



**Table 2.** Stage at diagnosis for all HCC cases by race/ethnicity and SES [% (95% CIs)].

	Local <i>n</i> = 21,916	Regional <i>n</i> = 12,062	Distant <i>n</i> = 7,958	Unstaged <i>n</i> = 3,853	<i>P</i> value <sup>a</sup>
<b>AI/AN</b>					
Total	44.1 (39.4–48.8)	30.2 (25.8–34.5)	17.4 (13.8–21.0)	8.4 (5.7–11.0)	
Low SES	48.1 (41.4–54.8)	25.0 (19.2–30.8)	17.9 (12.8–23.1)	9.0 (5.1–12.8)	<0.001
Medium SES	43.2 (35.4–51.0)	28.4 (21.3–35.5)	21.9 (15.4–28.5)	6.5 (2.6–10.3)	
High SES	32.8 (21.3–44.3)	51.6 (39.3–63.8)	4.7 (0.0–9.9)	10.9 (3.3–18.6)	
<b>Asian/PI</b>					
Total	51.0 (49.9–52.0)	26.4 (25.5–27.4)	15.6 (14.8–16.4)	7.1 (6.5–7.6)	
Low SES	45.8 (43.6–48.1)	28.0 (26.0–30.0)	18.4 (16.6–20.1)	7.8 (6.6–9.0)	<0.001
Medium SES	49.2 (47.3–51.0)	27.4 (25.8–29.1)	16.7 (15.4–18.1)	6.6 (5.7–7.6)	
High SES	55.2 (53.5–56.9)	24.7 (23.3–26.2)	13.1 (11.9–14.2)	7.0 (6.1–7.8)	
<b>Black</b>					
Total	43.9 (42.5–45.2)	27.6 (26.5–28.8)	20.1 (19.0–21.1)	8.5 (7.7–9.2)	
Low SES	43.6 (42.0–45.3)	27.9 (26.3–29.4)	20.3 (18.9–21.6)	8.2 (7.3–9.2)	0.323
Medium SES	43.2 (40.7–45.8)	27.4 (25.1–29.7)	20.8 (18.6–22.9)	8.6 (7.1–10.1)	
High SES	46.1 (42.4–49.9)	27.0 (23.7–30.3)	17.7 (14.8–20.5)	9.2 (7.0–11.4)	
<b>Latino</b>					
Total	49.3 (48.2–50.4)	25.7 (24.7–26.6)	16.7 (15.9–17.5)	8.4 (7.8–9.0)	
Low SES	47.9 (46.4–49.5)	25.3 (24.0–26.7)	17.8 (16.6–19.0)	9.0 (8.1–9.8)	0.149
Medium SES	50.7 (48.9–52.6)	25.8 (24.2–27.5)	15.5 (14.2–16.9)	7.9 (6.9–8.9)	
High SES	50.2 (47.6–52.8)	26.2 (23.9–28.5)	15.7 (13.8–17.6)	7.9 (6.5–9.3)	
<b>White</b>					
Total	47.3 (46.7–48.0)	26.2 (25.6–26.7)	17.6 (17.1–18.1)	8.9 (8.5–9.2)	
Low SES	46.8 (45.6–48.0)	25.7 (24.6–26.7)	18.6 (17.7–19.6)	8.9 (8.2–9.6)	0.007
Medium SES	47.2 (46.1–48.2)	26.4 (25.5–27.3)	18.0 (17.2–18.8)	8.4 (7.8–9.0)	
High SES	47.9 (46.9–49.0)	26.3 (25.4–27.3)	16.4 (15.6–17.2)	9.3 (8.7–9.9)	

<sup>a</sup>*P* value was obtained by comparing cancer stage distribution between low-SES and high-SES group by race/ethnicity.

## Discussion

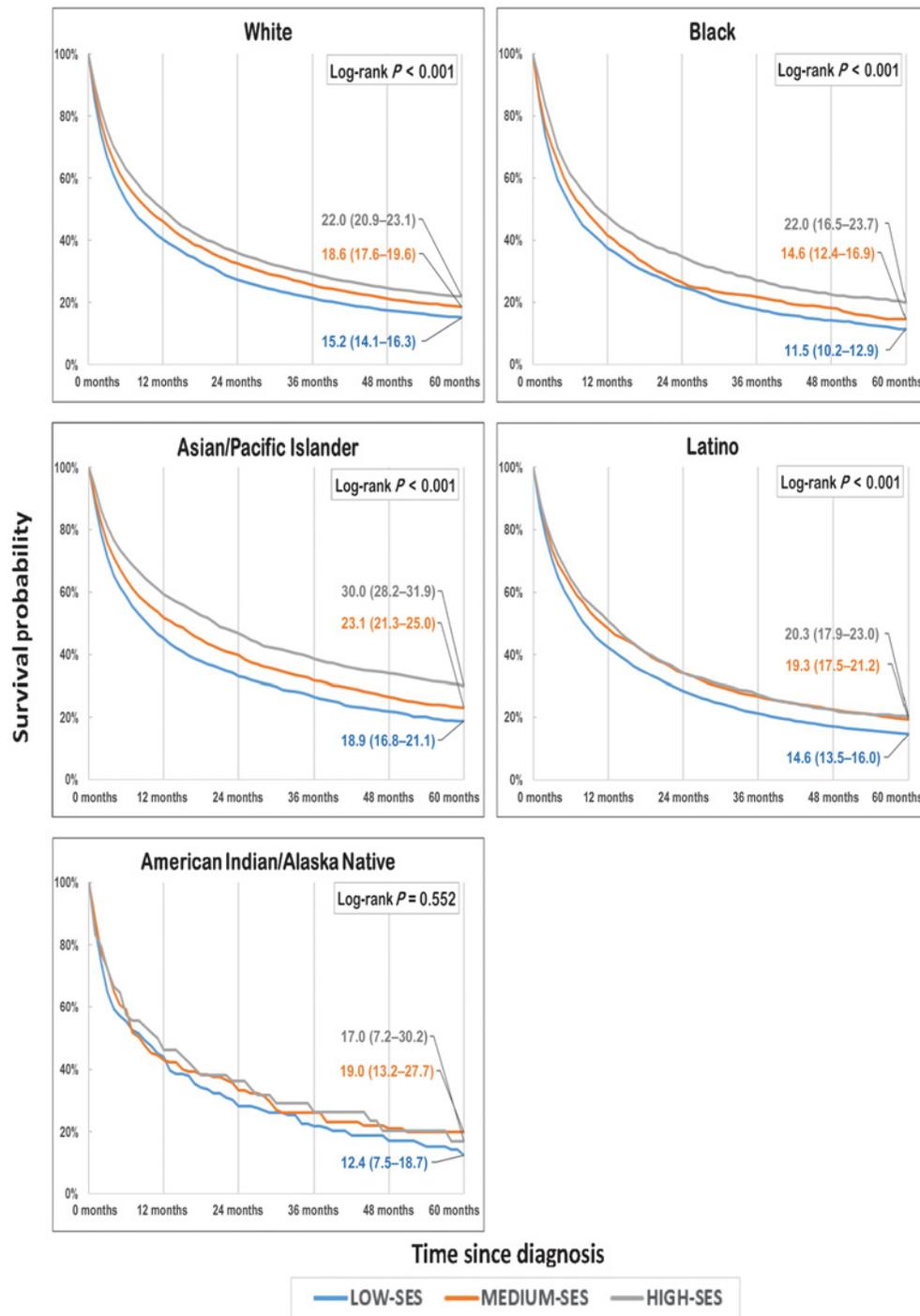
This study used a comprehensive and population-based approach to demonstrate that the burden of HCC is disproportionately experienced by low-SES populations in terms of incidence, stage at diagnosis, and 5-year survival, regardless of race/ethnicity and sex. Our findings expand the limited published research that has examined SEER data to investigate the association between certain HCC indicators and SES in the United States (11–13). One study used SEER-11 registry data to compare census tract neighborhood-level SES measures of incident HCC cases during 1996 and 2007 to the general population of the registry catchment area (11). They found that low neighborhood-level SES may be associated with greater HCC risk in specific racial/ethnic groups (11). These results are consistent with the fact that low SES, poverty, and low educational attainment have been associated with known risk factors for HCC, including obesity (18), metabolic syndrome (19), diabetes (20), heavy drinking (21, 22), and infection with HBV or HCV (23). Our study builds on this prior work by using the most recent SEER 18 registry, which includes more years of data and a substantially larger sample size (18,473 HCC cases from the SEER 11 registry areas vs. 45,789 HCC cases from SEER 18), and by comparing three major HCC indicators in five racial/ethnic groups, by SES and sex.

With few exceptions, our results indicate that HCC incidence was significantly greater among those with low-SES compared with those with high-SES for all race/ethnicities. In the total sample, and when stratified by sex, the highest incidence was observed among low-SES APIs and the lowest was found in high-SES Whites. Generally, HCC was highest among APIs, followed by AI/ANs, Latinos, Blacks, and Whites. This finding is consistent with recent publications that report a similar pattern of Whites having the lowest incidence of HCC, compared to other racial/ethnic

groups (7, 11, 13). The high incidence of HCC observed among APIs likely reflects the historical impact of HBV among this group. Chronic HBV is the most important cause of cirrhosis, HCC, and liver-related mortality among Asians worldwide (23).

Diagnosis of HCC at an early stage is a key contributor to favorable patient outcomes. We found that high-SES APIs had the highest percentage of HCC diagnosed at the local stage, whereas high-SES AI/ANs had the lowest. Although Blacks had a significantly lower incidence of HCC compared with the other racial/ethnic groups, they had the highest proportion of distant stage disease in both the low- and high-SES groups of all race/ethnicities. This result is consistent with studies demonstrating that Blacks in the United States are more likely to be diagnosed at a regional or distant stage for most cancers than Whites (24). The later stage at diagnosis for HCC observed among Blacks is a result of social determinants of health and structural racism that lead to health racial and ethnic inequities. These contributors include: (i) individual-level factors (e.g., differences in income education, and living conditions, health-related knowledge, and beliefs, hesitancy, and type of health insurance); (ii) provider-level factors (e.g., timely referrals and appropriate patient management, and discriminatory practices); and (iii) health system-level factors (e.g., accessibility and insurance coverage). All of these factors affect the type of access patients have to health care services, including preventive care and early detection services as well as treatment. Black patients and their health care providers may also be less likely to suspect liver disease and pursue timely liver cancer screening, compared to other patients such as APIs, who until recently, have had higher rates of HBV.

In recent years, HCC survival has improved as a result of earlier diagnosis and availability of medical interventions, such as early stage radiofrequency ablation, resection, and/or transplantation (25). Our analysis of SEER 18 data confirms that the five-year survival among



**Figure 2.** A comparison of 5-year survival for all HCC cases ( $n = 38,750$ ) by race/ethnicity and SES from 2000 to 2015. Differences by SES are presented as percentages and 95% CIs. Log-rank test was conducted to compare the survival curves among all SES groups by race/ethnicity.

low- and medium-SES Blacks is lower than in any other racial/ethnic group. This finding is consistent with a study that used SEER data from 1973 to 2006 to examine racial/ethnic and SES disparities in access to care and survival for 13,244 patients with early-stage HCC (12). The investigators found that Black and Latino patients received signifi-

cantly less invasive therapy than the API or White patients. After accounting for differences in stage, use of invasive therapy, and treatment benefit they found no racial/ethnic survival disparity between Latinos and Whites, but Blacks had persistently poor survival (14). Another study that investigated SES and racial/ethnic

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disparities in cancer found that Blacks had a higher mortality than Whites, regardless of SES group (26). The lower 5-year survival we observed among Blacks, compared with other racial/ethnic groups, is in part a consequence of the fact that their HCC was more likely to be diagnosed at a distant stage. The reduced observed survival among Blacks persists even after adjusting for surgery and stage at diagnosis, and is likely due to the aforementioned factors that are the result of systemic racist practices and policies that lead to gross health disparities.

This study has some limitations. The SEER 18 database represents approximately 28% of the U.S. population and does not include tumor data for all geographical regions. The age-adjusted liver cancer incidence rate reported by SEER 18 (5.0 per 100,000) is lower than the rate reported by the North American Association of Central Cancer Registries (7.9 per 100,000), which cover 99% of the U.S. population from 2012 to 2015 (27). Although our findings may not be as generalizable to all areas in the United States, our results and those of other investigators, indicate that the SEER population resembles the U.S. population with regard to race/ethnicity, as well as poverty and education (11). We included the AI/AN racial/ethnic group in our analyses because they are an understudied population at high-risk of HCC (28). However, certain estimates for this group (e.g., stage at diagnosis for AI/AN women) may be unstable due to small sample sizes (1% of the sample). Despite the sample size limitations, we think it is important to report the AI/AN results. Another limitation is that we did not disaggregate the API and Latino groups by ethnicity, which should be examined to identify further disparities by SES and sex among these subgroups. HCC has many possible etiologies that can vary based on different cultural norms and behaviors in racial/ethnic subgroups, so it is very important to conduct future analyses that will allow us to uncover these disparities in more detail. We also were unable to determine the impact of recent immigration or acculturation on HCC incidence, stage at diagnosis, and 5-year survival, among APIs and Latinos because these data are not available in the SEER 18 dataset. Future studies should consider a more detailed analysis of larger Asian or Latino subgroups as well as their nativity and immigration status. Acculturation, nativity, and immigration status are proximal determinants of health that affect individuals' health behaviors by way of culture, and should be closely examined to identify how they may contribute to disparities in HCC incidence, stage, and survival in API and Latino subgroups (29). For example, some more recent API or Latino immigrants might have specific risk factors for HCC (e.g., HBV infection or heavy alcohol consumption), or they may be unable to access primary and specialty care services, which could lead to worse health outcomes. Future research is necessary to shed light on how recent immigration or acculturation among APIs and Latino subpopulations may have an impact on observed disparities in HCC incidence, stage and survival. The SEER 18 dataset is also limited to a specific time period (2000 to 2015), and the lag in availability of cancer data may not reflect current trends. We used census tract-level data from the SEER specialized database as a proxy for SES of the HCC cases. Census tract-level information may not accurately represent individual patient characteristics and does not include information about certain factors that influence outcomes, such as insurance status. Also, the characteristics of the HCC cases and the individuals who live in a certain census tract may differ from each other, so our results should be interpreted with caution. Although SEER data poses some challenges, it continues to be the best source of long-term cancer information in the United States and is one of the few available cancer

databases that can be used to investigate cancer health disparities at a national level.

Our study has several important strengths. First, we used a large, national population-based cancer registry database with more than 45,000 incident cases of HCC, to determine differences in incidence, stage, and survival by race/ethnicity and SES. Second, it is unique in the literature because it demonstrates that among all racial/ethnic groups (except AI/AN), individuals with low-SES have higher HCC incidence, distant stage at diagnosis, and poor survival than those with high-SES. SEER also provides access to long-term data on these indicators, which may reflect the impact of national programs and interventions on HCC outcomes. Third, the SEER 18 SES variable was determined as a composite score for each census tract by conducting a factor analysis from seven key variables, which now serves as a valuable tool for monitoring disparities in cancer burden (16). Fourth, our work builds on prior studies by using a more comprehensive approach to investigate how the interplay of race/ethnicity, SES, and sex contribute to existing disparities in HCC incidence, stage at diagnosis, and 5-year survival. Increasing evidence suggests that a better understanding of the intersection between race/ethnicity, SES, and sex is likely necessary to mitigate inequalities (30, 31).

In summary, our findings uncover significant SES disparities in HCC incidence, stage at diagnosis, and 5-year survival, across race/ethnicity and sex. These disparities are likely contributing to the growing HCC mortality rates over the past decades. Our results provide a better understanding of the interplay between SES and race/ethnicity for three key HCC indicators, which may help inform future research, health policy, as well as prevention and control strategies. The findings of this study should be used to develop HCC prevention and control efforts that address the specific needs of low-SES populations, in addition to specific racial/ethnic groups that have a greater risk of HCC. We also hope that our findings will contribute to the development of guidelines for surveillance to detect HCC at an earlier stage among high-risk patients, such as Black males. This study also contributes to ongoing efforts to identify ways to close gaps in health outcomes by race and ethnicity in the United States.

### Authors' Contributions

**Y.N. Flores:** Conceptualization, formal analysis, methodology, writing—original draft, writing—review and editing. **G.D. Datta:** Formal analysis, methodology, writing—original draft, writing—review and editing. **L. Yang:** Data curation, formal analysis, methodology, writing—original draft, writing—review and editing. **E. Corona:** Conceptualization, formal analysis, writing—review and editing. **D. Devineni:** Investigation, writing—review and editing. **B.A. Glenn:** Writing—review and editing. **R. Bastani:** Writing—review and editing. **F.P. May:** Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, investigation, methodology, project administration, writing—review and editing.

### Acknowledgments

This study was supported by the Jonsson Comprehensive Cancer Center [NIH/NCI, P30CA16042 (Teitell PI)], Cancer Center Core Grant, UCLA-Kaiser Permanente Center for Health Equity, and the Vatche and Tamar Division of Digestive Diseases at UCLA. Y.N. Flores was supported by NIH/NCI K07CA197179.

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Received July 17, 2020; revised October 9, 2020; accepted March 11, 2021; published first March 18, 2021.

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