DISPARITIES IN TREATMENT UTILIZATION, DELAY AND OUTCOMES AMONG PATIENTS WITH HEPATOCELLULAR CARCINOMA IN THE UNITED STATES

A Dissertation

by

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death in the United States (US). Racial-ethnic minority groups are at a greater risk of treatment underutilization and delay, along with worse outcomes. Prior published literature in other cancers like lung, colorectal, prostate indicates that social determinants of health (SDOH) like lower neighborhood SES are associated with worse survival. However, the interplay between race, ethnicity, and SDOH has not been well explored among HCC patients.

Therefore, this dissertation aims to (1) characterize and quantify racial-ethnic disparities in treatment receipt among patients with HCC through a meta-analysis; (2) characterize the interaction of racial, ethnic, and neighborhood socioeconomic disparities in curative treatment use and overall survival in the US among a large population-based sample of patients with HCC (3) describe the prevalence and disparities in HCC treatment delay and evaluate the association between treatment delay and overall survival in a large population-based sample of patients with HCC in the US.

Results from the first study indicate that Black and Hispanic patients had a lower pooled odds ratio (OR) for receipt of curative treatment when compared to White patients. Additionally, Black patients had lower pooled OR for receiving any HCC-specific treatment when compared to White patients.

Results from the second study indicate that curative treatment was underutilized among HCC patients. Additionally, Black patients living in high poverty neighborhoods

had lower odds of receiving curative treatment and worse survival when compared to white patients living in similar neighborhoods.

Results from the third study indicate that Black patients and those living in high poverty neighborhoods had higher odds of receiving delayed treatment. Subsequently, delayed treatment was associated with worse overall survival.

Neighborhood poverty level may be a mediating factor adding to persisting racial-ethnic disparities in treatment receipt. Additionally, racial-ethnic disparities persist among treatment delays. Future studies should aim at understanding the role of various SDOH in the HCC care continuum to be able to design interventions that reduce these disparities and achieve equitable outcomes among traditionally marginalized groups in the US.

DEDICATION

To my mother and father, Leena Kamat-Wagle and Sandeep Wagle, for supporting me their entire lives. I am because you are.

To Abhishek, thank you for being invested in my life and supporting me throughout my dissertation journey and beyond. Love you babe!

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Data for chapters 3 and 4 were constructed in collaboration with Sulki Park (Department of Industrial and Systems Engineering).

All other work conducted for the dissertation was completed by the student independently.

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NOMENCLATURE

AASLD	American Association for the Study of Liver Diseases
AFP	Alpha-fetoprotein
AJCC	American Joint Committee on Cancer
ALD	Alcoholic Liver Disease
BCLC	Barcelona Clinic Liver Cancer
CI	Confidence Interval
CPL	Census tract Poverty Level
CPT	Current Procedural Terminology
EASL	European Association for the Study of the Liver
EBRT	External Beam Radiation Therapy
ECOG	Eastern Cooperative Oncology Group
ETOH	Alcohol use
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCPCS	Healthcare Common Procedure Coding System
HCV	Hepatitis C Virus
HR	Hazard Ratio
ICD-O	International Classification of Diseases for Oncology
ICD-9	International Classification of Diseases, 9th revision
ICD-10	International Classification of Diseases, 10th revision

MAFLD	Metabolic Associated Liver Disease
MELD	Model for End-stage Liver Disease
NAFLD	Nonalcoholic Fatty Liver Disease
NASH	Nonalcoholic Steatohepatitis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIH	National Institutes of Health
OLT	Orthotopic liver transplantation
OR	Odds Ratio
RCT	Randomized Control Trial
RFA	Radiofrequency Ablation
SBRT	Stereotactic Beam Radiation Therapy
SDOH	Social Determinants of Health
SES	Socioeconomic Status
SEER	Surveillance, Epidemiology and End Results
TACE	Transarterial Chemoembolization
TARE	Transarterial Radioembolization
US	United States

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1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for around 80% of all primary liver cancers. [1,2] Its incidence has tripled over the past three decades and is one of the fastest rising causes of cancer-related mortality in the United States (US). [3] According to Surveillance, Epidemiology, End Results (SEER) registry projections, HCC incidence will continue to rise with the greatest increase among Hispanics, followed by Black patients in 2030.[4] The five-year survival for HCC remains below 20% but can be as high as 70% in early-stage HCC patients who receive potentially curative treatment (liver transplantation, surgical resection, local ablation).[1] Even with the high benefit of potentially curative treatment, it remains underutilized, especially among the racial-ethnic minority groups like Black and Hispanic patients in the US, which have higher HCC incidence and mortality rates. [5–7] Studies have shown that Black and Hispanic patients have lower odds of receiving curative treatment, i.e., transplantation, surgical resection, local ablation, and worse overall survival. [8–12]

Social determinants of health (SDOH) have 5 main domains: economic stability, education access and quality, health care access and quality, and social and community context.[13] SDOH are likely to have an additive effect on persisting racial-ethnic disparities in access to care and subsequent worse health outcomes (Error! Reference s ource not found.).[13–15] The stress caused by these determinants may have negative multi-generational impacts on health.[16] According to a recent systematic review by Coughlin,

SDOH like poverty, lack of education, immigration status, social isolation seemed to worsen survival in breast and colorectal cancer patients.[17,18]

Figure 1. SDOH domains.[19]

Examining published literature on the HCC care continuum, it has been found that limited studies examine the intersectionality of race, ethnicity, and SDOH and its impact on the HCC care continuum.[20,21] However, published studies on lung, ovarian, breast, prostate, and colorectal cancer have shown that SDOH like neighborhood disadvantage or lower neighborhood SES has been associated with poorer survival

among these cancer patients. [22–26] However, the impact of neighborhood SES and its interaction with race-ethnicity on receiving HCC treatment has not been studied well.

In addition to underuse, downstream failures like delays in receiving treatment persist within the HCC care continuum.[27,28] Racial-ethnic minorities may be more prone to experiencing delays in receiving treatment.[27,28] To our knowledge, most studies that describe the prevalence of treatment delay and examine its association with overall survival among HCC patients are single or multi-center, limiting their generalizability beyond those settings.[27–29] Additionally, there are no consistent findings among published studies on whether HCC treatment delay is associated with worse survival. [27–29] Understanding the effect of social SDOH on the HCC care continuum and overall survival, particularly among racial-ethnic minority patients, is necessary to achieve equitable health outcomes. [13,19]

Hence, this dissertation aims to (1) characterize and quantify racial-ethnic disparities in treatment receipt among patients with HCC in the United States through a meta-analysis; (2) characterize the interaction of racial, ethnic, and neighborhood socioeconomic disparities in curative treatment use and overall survival in the United States among a large population-based sample of patients with HCC (3) Describe the prevalence and disparities in HCC treatment delay and evaluate the association between treatment delay and overall survival in a large population-based sample of patients with HCC in the United States.

2. A META-ANALYSIS OF RACIAL-ETHNIC DISPARITIES IN TREATMENT RECEIPT AMONG HEPATOCELLULAR CARCINOMA PATIENTS IN THE UNITED STATES

2.1. Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for around 80% of all primary liver cancer. [1,2] It is one of the fastest rising causes of cancer-related deaths in the United States (US). [3] Receipt of curative (transplantation, surgical resection, local ablation) is known to offer a good survival benefit among early-stage HCC patients; however, it remains underutilized.[30–33] Even though there are substantially higher rates of HCC incidence and mortality among Black and Hispanic patients when compared to non-Hispanic white patients, potentially curative treatment continues to remain underutilized in these populations. [5–8,30–33] Moreover, underutilization in HCC treatment is linked to worse overall survival.[30–33]

The process from HCC diagnosis to receipt of treatment is complex, and disparities can occur within the entirety of this continuum. According to a recent systematic review by Rich et al. (2020), racial-ethnic disparities persisted in early HCC detection and overall survival. Black patients had worse overall survival and lower odds of early-stage HCC when compared to White patients.[21] Additionally, another systematic review indicated that HCC surveillance was associated with an increase in early-stage detection and better curative treatment receipt.[34] Furthermore, according to the systematic review and meta-analysis by Tan et al. (2013), only 21.8% of patients

received curative treatment across 23 studies with a total of 50,769 patients.[20] However, they did not quantify racial-ethnic disparities in receiving HCC treatment.

In our understanding, no meta-analysis has been published in recent years seeking to characterize and quantify racial and ethnic disparities in HCC treatment receipt. To identify strategies that seek to reduce disparities in treatment receipt, it is critical to deepening our understanding of existing disparities within the HCC care continuum. Therefore, our meta-analysis aims to (1) characterize and quantify racial-ethnic disparities in treatments among patients with HCC in the United States

2.2. Methods

2.2.1. Search Strategy

We adhered to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[35] We searched three electronic databases: MEDLINE (Ovid), Embase (Ovid), and CINAHL from January 2012 to December 2020. Broadly, the search terms captured studies mentioning ((hepatocellular or liver) adj2 (carcinoma or neoplasm* or cancer*)) AND (surgery or treatment* or therap* or chemoemboliz* or chemoembolis* or chemotherap* or sorafenib or nexavar or radiofrequency ablation or rfa). We also applied a validated health equity filter to capture disparity-focused studies within the HCC literature.[36] We used Web of Science (Clarivate Analytics) to search references and citations of the included studies.

2.2.2. Eligibility Criteria

One investigator screened the articles in two phases using Covidence, first by title and abstract and then by full text.[37] Studies with the following characteristics were

included, (1) adult patients diagnosed with HCC; (3) receipt of HCC specific treatment as the study objective; (4) captured racial-ethnic differences between HCC specific treatment and no treatment; (4) published during January 2012 to January 2021. A second reviewer consulted if inclusion was unclear, and inclusion was determined by consensus between two reviewers. We excluded studies with the following characteristics: (1) the study was conducted outside of the United States; (2) published in a language other than English; (3) the study did not have original data (e.g., literature review, letter to the editor, editorial or commentary); (4) the study had non-human data.

2.2.3. Data Extraction and Risk of Bias Assessment

Data extraction was be conducted by one reviewer. A second investigator was able to address clarification when needed. Data was collected on study years, study setting, number of HCC patients in each study, tumor staging used, definitions of HCC treatment, HCC treatment rates, crude and adjusted odds ratio estimate for receipt of curative treatment and any treatment, liver disease etiology, indicators of advanced liver disease, Additionally, we used the progress-plus framework to extract information on the reporting of correlates like age, sex, geographic factors, socioeconomic status, and insurance.[38] Two investigators were involved in assessing the risk of bias of the included studies using the NIH quality assessment tool for observational cohort and cross-sectional studies.[39]

2.2.4. Outcomes and Statistical Analysis

Our primary study outcome was the receipt of treatment. Curative treatment was defined as receiving local ablation, surgical resection, liver transplantation. Any

treatment was defined as receiving curative treatment and non-curative treatment (embolization, radiation, systemic chemotherapy). To evaluate racial and ethnic disparities in receipt of treatment, we recorded crude and adjusted ORs and 95% confidence intervals from each study for Black, Asian, and Hispanic patients compared to White patients. We preferably used adjusted ORs in our analysis. We calculated pooled OR estimates using the DerSimonian–Laird method for a random effects model. We performed subgroup analysis for the study setting (population vs academic/hospital based cohorts). We evaluated heterogeneity by utilizing forest plots and I^2 statistic. An I^2 >75% indicated a high level of heterogeneity, whereas I^2 values between 50% and 75% indicated moderate heterogeneity. The risk of publication bias was evaluated by inspecting funnel plots and calculating Egger's test.

Our secondary outcome was the HCC treatment rate (any treatment and curative treatment). Proportions of patients who received HCC-specific treatment were calculated. All treatment rates were weighted based on patients receiving treatment relative to the entire study sample. DerSimonian–Laird method was used for a random effects model. We evaluated heterogeneity by utilizing forest plots and I^2 statistic.

Data analysis was performed using Stata 17 (StataCorp, College Station, TX) and R programming software (R Development Core Team, 2017).

2.3. Results

The initial search yielded 8554 articles, out of which 1305 duplicates were removed. 7249 titles and abstracts were screened to yield 338 full-text articles.2 more articles were added to the full-text review through forward and backward citation. 23

studies had information on racial-ethnic disparities related to receipt of treatment; however, due to overlapping cohorts, only 13 of those studies were included in the meta-analysis. (**Figure 2**)

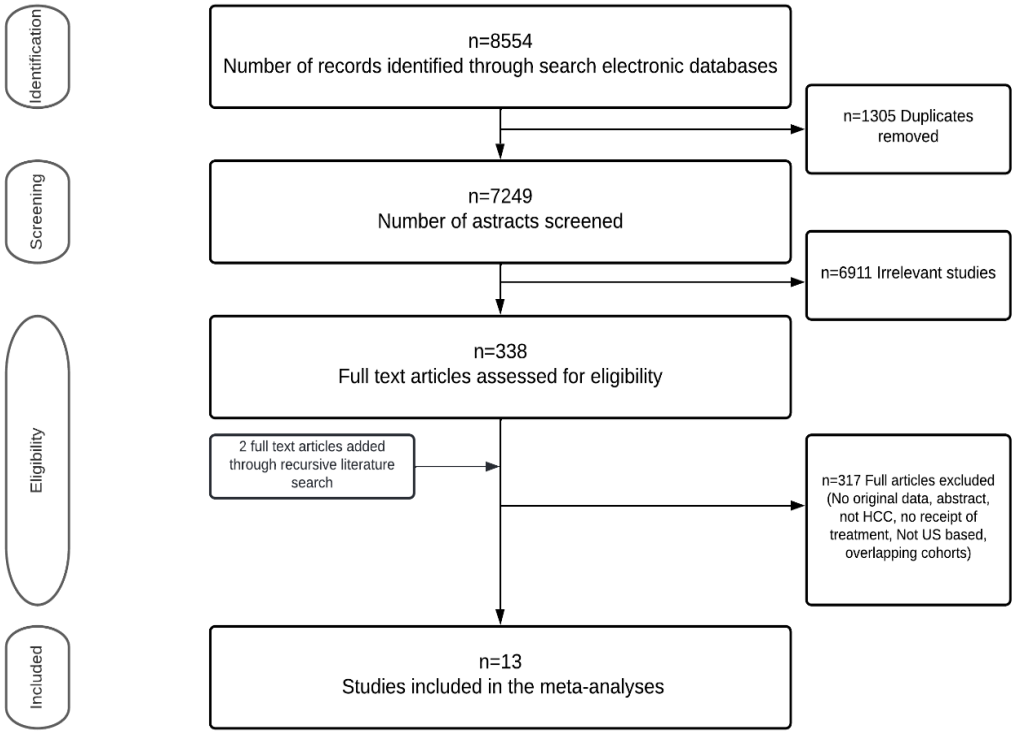

Figure 2. PRISMA flow.

2.3.1. Characteristics of included studies

All the included studies had retrospective cohort study design. Most studies utilized a population-based cohort as outlined in Table 1. 4 studies were single-center studies, whereas 3 were multi-center. Study years varied from 1998 to 2017. Sample

sizes varied from 267 to 143692 patients. Additionally, only 1 study examined the disparities between ethnicities among Asians receiving treatment.

Table 1. Study characteristics.

Study	Study years	Number of HCC patients	Database/ Study setting	Race/ethnicity examined in the studies	Treatment disparities examined in the meta-analyses
Kanwal et al., 2012[40]	2001 - 2007	267	Liver Cancer Research Network (LCRN)	White, Black, Other	Curative (Black), Any treatment (Black)
Wong et al., 2012[41]	NR	575	Hawaii Medical Center-East	White, Asian, Pacific Islander	Curative (Asian)
Davila et al., 2013[31]	1998 - 2006	1296	VA Hepatitis C Clinical Case Registry	White, Black, Hispanic, Asian, Missing	Any treatment (Black)
Singal et al., 2013[28]	January 2005 - June 2012	267	Parkland Health & Hospital System	White, Black, Hispanic, Asian	Any treatment (Black)
Wong et al., 2014[42]	1998 - 2014	60772	SEER database	White, Black, Asian, Hispanic	Curative (Black, Asian, Hispanic)
Hoehn et al., 2015[43]	1998 - 2011	143692	National Cancer Database	White, Black, Asian, Other	Curative (Black, Asian)
Chidi et al., 2016[12]	January 1, 2006 – December 31, 2011	3576	Pennsylvania Cancer Registry	White, Black, Hispanic, Asian, Other/Unknown	Curative (Black, Asian, Hispanic)
Sarpel et al., 2016[11]	2003 - 2013	754	Mount Hospital	White, Black, Hispanic, Asian	Curative (Black, Asian, Hispanic)

Table 1. Continued.

Study	Study years	Number of HCC patients	Database/ Study setting	Race/ethnicity examined in the studies	Treatment disparities examined in the meta-analyses
Stewart et al., 2016[10]	January 1, 1988-December 31, 2012	33270	California Cancer Registry	White, Black, Hispanic, Cambodian, Chinese, Flilpino, Hawai'ian/Pacific Islander, Japanese, Korean, Laotian/Hmong, Other Asian, South Asian, Thai, Vietnamese	Curative (Black, Hispanic)
Kokabi et al., 2017[44]	2000 - 2010	9368	SEER-Medicare linked database	White, Black, Asian, Hispanic, Other	Any treatment (Black)
Dakhoul et al., 2019[45]	January 2000 – June 2014	1196	Indiana University Academic Medical Center	White, Black	Curative (Black)
Rich et al., 2019[8]	January 2008 – July 2017	1117	Parkland Memorial Health and Hospital System, and the University of Texas Southwestern Medical Center	White, Black, Hispanic	Curative (Black, Hispanic)

Table 1. Continued.

Study	Study years	Number of HCC patients	Database/ Study setting	Race/ethnicity examined in the studies	Treatment disparities examined in the meta-analyses
Scaglione et al., 2020[9]	June 2012 - May 2013	379	4 U.S. centers (University of Michigan, Loyola, Parkland, Ben Taub)	White, Black, Hispanic, Other	Curative (Black, Hispanic)

2.3.2. Receipt of treatment

7 studies examined curative treatment (Transplantation, surgical resection and/or local ablation) receipt only[10–12,41–43,45] 6 studies included a combination of curative and non-curative (Embolization, systemic chemotherapy and/or radiation) treatments.[8,9,28,31,40,44] Definitions for curative and any HCC treatment for each study are provided in **supplemental tables 1 and 2** in Appendix A.

2.3.3. Clinical predictors

5 studies used a combination of BCLC staging and Milan criteria or SEER staging and Milan criteria as the tumor staging system (**Table 2**). 4 studies used either BCLC or AJCC staging. One study did not report on the tumor staging criteria used, whereas the remaining two studies included patients with specific tumor stage. 8 out of 13 studies examined liver disease etiology, with HCV and HBV being the most reported etiologic risk factors. Only 6 out of 13 studies reported proxies of advanced liver disease indicators like ascites and hepatic encephalopathy. Only 3 studies reported underlying cirrhosis for the patients.

Table 2. Clinical study characteristics.

Study	Tumor staging system	Early-stage (%)	Cirrhosis (%)	Liver disease etiology examined	Advanced liver disease predictors
Kanwal et al., 2012[40]	BCLC stage	28%	NR	Viral hepatitis, Non-viral hepatitis	Ascites
Wong et al., 2012[41]	NR	NR	NR	HCV, HBV, Excess alcohol use	NR
Davila et al., 2013[31]	BCLC stage	Any HCC treatment (14.6%), No HCC treatment (5.5%)	NR	NR	Ascites, Hepatic Encephalopathy, Varices
Singal et al., 2013[28]	BCLC stage, Milan criteria	BCLC stage A (15%), Unifocal disease (52%)	Yes	HCV, HBV, ALD, NAFLD	Child Pugh class, Ascites, Hepatic Encephalopathy
Wong et al., 2014[42]	SEER stage, Milan criteria	1998 – 2003: Localized stage (45%), within Milan (22.8%). 2004 – 2008: Localized stage (50.4%), within Milan (31.8%); 2009 – 2010: Localized stage (51.7%), within Milan (37.1%)	NR	NR	NR
Hoehn et al., 2015[43]	AJCC clinical stage, AJCC pathological stage	Clinical stage White (25.5%), Black (23.1%), Asian (24.9%)	NR	NR	NR
Chidi et al., 2016[12]	SEER stage	Localized (55.3%)	NR	NR	NR
Sarpel et al., 2016[11]	N/A	N/A	NR	HCV, HBV, ALD, NASH, Other	NR
Stewart et al. 2016[10]	SEER stage	Localized stage by ethnicity	NR	NR	NR

Table 2. Continued.

Study	Tumor staging system	Early-stage (%)	Cirrhosis (%)	Liver disease etiology examined	Advanced liver disease predictors
Kokabi et al., 2017[44]	AJCC stage	Stage I (26.1%)	NR	HCV, HBV, ALD, Other	NR
Dakhoul et al., 2019[45]	BCLC, Milan criteria	BCLC Stage A: White (25%), Black (24%) Within Milan: White (42%), Black (48%)	White (92%), Black (88%)	HCV, HBV, NAFLD, Autoimmune diseases, Metabolic liver diseases	Proportion of Child Pugh Class C
Rich et al., 2019[8]	BCLC stage, Milan criteria	BCLC Stage 0 (5.5%), BCLC Stage A (35.8%)	Child C cirrhosis (72%)	HBV, HCV, ALD, NASH/cryptogenic	Child Pugh Class, Hepatic encephalopathy, Ascites
Scaglione et al., 2020[9]	BCLC, Milan criteria	Within Milan (46.4%), BCLC stage 0 (6.6%), BCLC stage 1 (24.3%)	Yes	HBV, HCV, NASH, ETOH	Child Pugh Class, Ascites

2.3.4. SES and geographic covariates included in multivariable analysis of receipt of treatment

7, 7, 5, and 6 studies controlled for SES, insurance, education, and geographic factors, respectively, in the multivariable analysis of receipt of treatment (**Table 3**). Studies that controlled for SES mostly used the median household income to indicate SES. However, 2 studies used a different measure of SES. Scaglione et al. used insurance as a proxy for SES.[9] Stewart et al. used neighborhood SES index calculated by incorporating education index, median household income, proportion below 200% of the poverty level, median rent, median house value, proportion with a blue-collar job, and proportion older than 16 in the workforce without a job.[10] Davila et al. controlled for geographic regions but did not control for SES, insurance, and education.[31]

Only 3 studies controlled for geographic region along with insurance, education, and SES. However, none of the studies examined at the interaction between race, ethnicity, and SES and its impact on receipt of HCC-specific treatment.

Table 3. SES and geographic covariates included in multivariable analysis of receipt of HCC treatment.

Study	SES	Insurance status	Education	Geographic factors
Kanwal et al., 2012[40]	NR	NR	NR	NR
Wong et al., 2012[41]	Median income (based on zip code, based on education)	None, Private, Medicare, Medicaid	Years of education completed	Oahu, Non-Oahu
Davila et al., 2013[31]	NR	NR	NR	Geographic region (Northeast, Midwest, South, West, Puerto/Virgin Islands)
Singal et al., 2013[28]	NR	NR	NR	NR
Wong et al., 2014[42]	NR	NR	NR	NR
Hoehn et al., 2015[43]	Median household income (based on zip code)	Uninsured, Private, Medicare, Medicaid, Other	Percent of adults in the patient's zip code without a high school degree	Metro, Urban, Rural; Distance traveled for treatment
Chidi et al., 2016[12]	Median household income	NR	Percent high school graduates	Rurality, proximity to high-volume surgical center within 30 mins
Sarpel et al., 2016[11]	Median income	None/Other, Commercial+supplement, Government only	NR	NR
Stewart et al., 2016[10]	Neighborhood SES	NR	Aggregate SES measure utilizes education component	Regions in California

Table 3. continued

Study	SES	Insurance status	Education	Geographic factors
Kokabi et al., 2017[44]	Median household income	Even though all Medicare beneficiaries were captured, having Medicaid was captured.	Census tract education	Geographic region; Urban, Rural/less urban
Dakhoul et al., 2019[45]	NR	Private, Medicare, Medicaid, Self-pay	NR	NR
Rich et al., 2019[8]	NR	Commercial insurance, Medicare, Medicaid, Parkland financial assistance	NR	NR
Scaglione et al., 2020[9]	Insurance used as a proxy for SES	Uninsured, Commercial, Medicare, Medicaid, Subsidy	NR	NR

2.3.5. Racial-ethnic disparities in receipt of treatment

9 studies (n=247347) assessed disparities in receipt of curative treatment: 9 (n=247347) Black-White, 5 studies (n=211693) Asian-White and 6 studies (n=102192) Hispanic-White.[8–12,40–43,45] Additionally, Black-White disparities in receipt of any treatment were examined through 4 studies (n=11198).[28,31,40,44] On visual inspection of funnel plots, it was difficult to point asymmetry due to a limited number of studies. However, we found no evidence of publication bias by Egger's test (p>0.1)

Black patients had lower odds of receipt of curative treatment when compared to White patients (pooled OR 0.65, 95% CI 0.52 – 0.82) (**Figure 3**). The test of H_0: $\theta = 0$ with the z-test statistic of -3.68 and the p-value of <0.05 suggested that the overall mean estimate was statistically significantly different from 0. Moderate heterogeneity was observed with I^2 statistic of 70.7%. There was a presence of between-study heterogeneity (p<0.05).

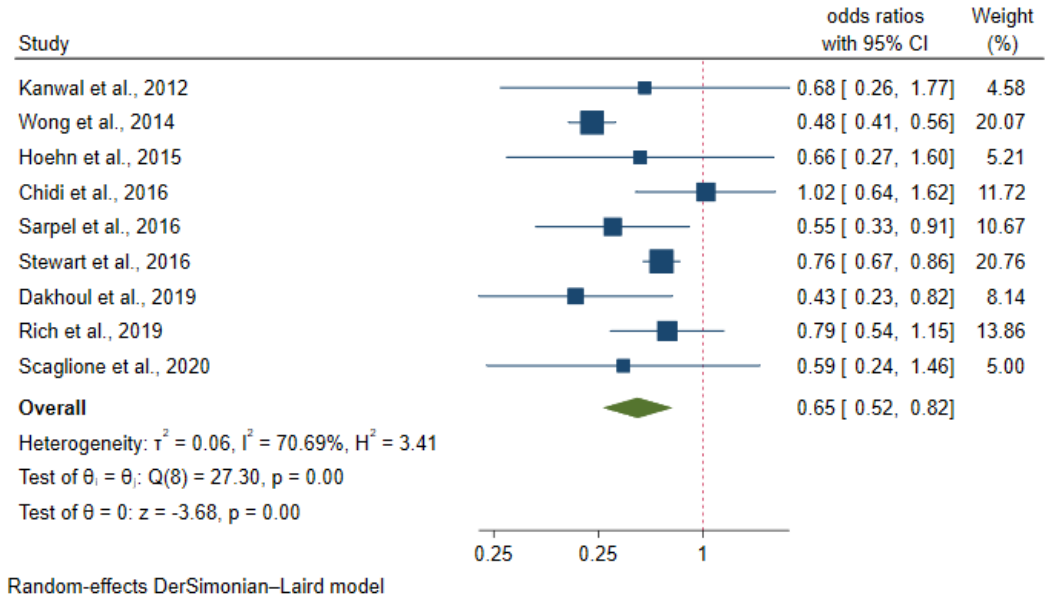

Figure 3. Odds of receipt of curative treatment in Black vs White patients (reference).

Additionally, Black patients had lower odds of receipt of any treatment when compared to White patients (pooled OR 0.70, 95% CI 0.57 – 0.86) (**Figure 4**). The test of H_0: $\theta = 0$ with the z-test statistic of -3.38 and the *p*-value of <0.05 suggest that the overall mean estimate is statistically significantly different from 0. There was no presence of between-study heterogeneity (I^2 statistic 33%; *p*=0.21).

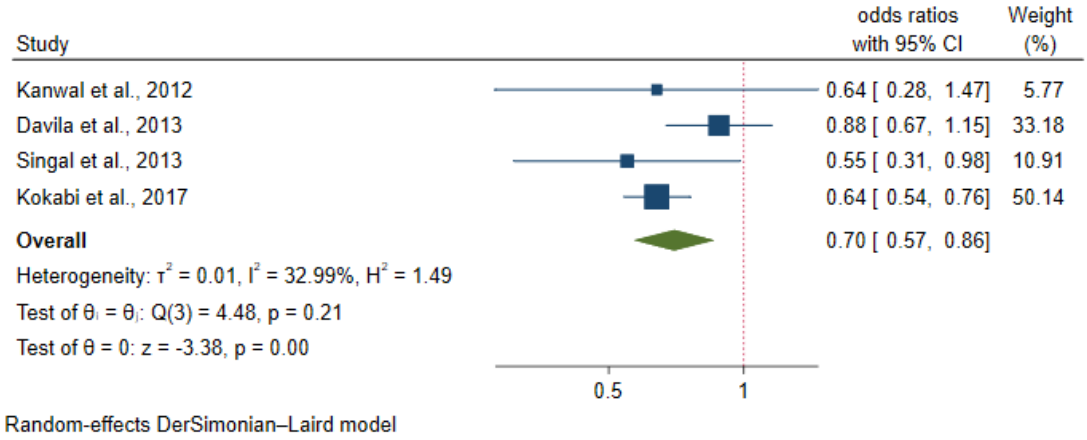

Figure 4. Odds of receipt of any treatment in Black vs. White patients (reference).

6 studies (n=102192) were included to examine Hispanic-White disparities in curative treatment receipt. Hispanic patients had lower odds of receipt of curative treatment when compared to White patients (pooled OR 0.77, 95% CI 0.72 – 0.82) (**Figure 5**). The test of H0: $\theta = 0$ with the z-test statistic of -8.34 and the p-value of <0.05 suggest that the overall mean estimate was statistically significantly different from 0. However, the data should be interpreted with caution since we had only 6 studies to estimate Hispanic-White disparities. The test of homogeneity was not statistically significant, i.e., we could not accept the presence of between-study heterogeneity (I^2 = 0%, *p*=0.81).

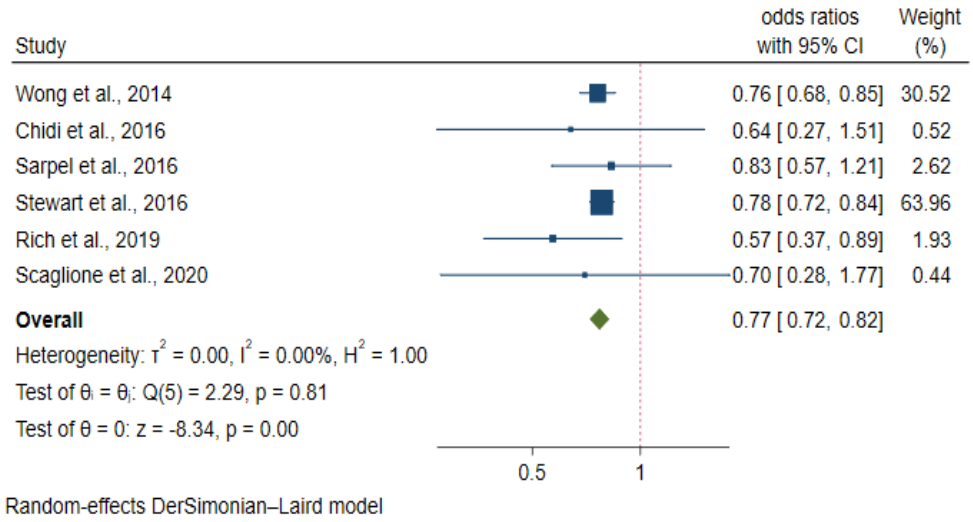

Figure 5. Odds of receipt of curative treatment in Hispanic vs. White patients (reference).

Data were insufficient to calculate the pooled odds ratio for receipt of any treatment among Hispanic patients compared to White patients.

In the subgroup analysis for Black-White disparities in curative treatment receipt, cohort-specific overall effect sizes were not statistically different (p=0.695) (**Supplemental Figure 4**, Appendix A).

5 studies (n=211693) were included to examine Asian-White disparities in curative treatment receipt. Asian patients had lower odds of receipt of curative treatment when compared to White patients (pooled OR 0.73, 95% CI 0.50 – 1.08) (**Figure 6**). The test of H0: $\theta = 0$ with the z-test statistic of -1.56 and the p-value of 0.12 suggest that the overall mean estimate was not statistically significantly different from 0. The test of

homogeneity was not statistically significant, i.e., we could not accept the presence of between-study heterogeneity (I^2 = 56.7%, *p*=0.06).

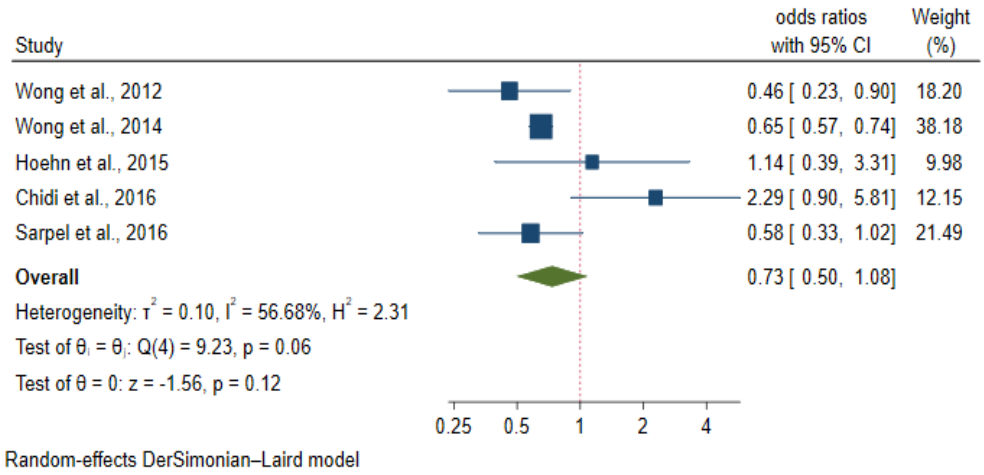

Figure 6. Odds of receipt of curative treatment in Asian vs. White patients (reference).

Additionally, data were insufficient to calculate the pooled odds ratio for receipt of any treatment among Asian patients compared to White patients.

Data were insufficient for subgroup analysis of study settings in Asian-White and Hispanic-White analyses. Additionally, included studies did not have sufficient data to calculate Native American-White disparities in receipt of curative and any HCC treatment.

2.3.6. Treatment utilization

10 (n=245698) studies assessed the rate of curative treatment among patients with HCC. Curative treatment rates ranged from 9.7% to 45.7%, with a pooled treatment rate of 24.8% (95% CI 22.8 – 26.9, p<0.05). The test of H_0: $\theta = 0$ with the z-test statistic of 7.28 and the p-value of <0.05 suggest that the overall mean estimate was statistically significantly different from (**Figure 7**).

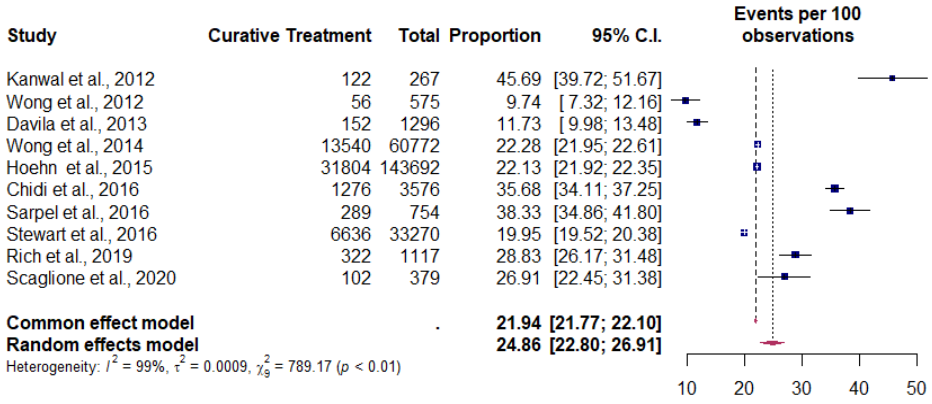

Figure 7. Pooled curative treatment rate for HCC patients.

4 (n=3059) studies assessed the rate of any treatment among patients with HCC. Any treatment rate ranged from 34.3% to 69.9% with a pooled treatment rate of 57.9% (95% CI 38.7% - 77.1%). The test of H_0: $\theta = 0$ with the z-test statistic of 7.11 and the p-

value of <0.05 suggest that the overall mean estimate was statistically significantly different from (**Figure 8**).

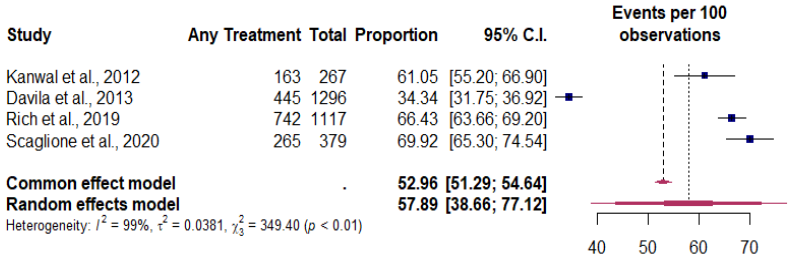

Figure 8. Pooled any treatment rate for HCC patients.

2.4. Risk of bias assessment

We used the NIH quality assessment tool to examine the quality and the risk of bias of studies included in the meta-analysis, as outlined in **Table 4.** All the studies were retrospective in nature, raising the potential for omitted variable bias and making it challenging to examine causal relationships between the exposure and the outcome. None of the studies accounted for multiracial individuals. Studies that were conducted in

single centers introduced selection bias and had limited generalizability outside of that setting. Studies utilizing only the SEER database could not include granular data on HCC prognostic factors, Eastern Cooperative Oncology Group (ECOG) performance status, and laboratory levels. 9 studies could not adjust for Child-Pugh class, a robust indicator of advanced liver disease. 10 studies did not report on loss to follow-up information. 6 studies did not control for SES, an important social determinant of health that likely affects receipt of HCC treatment.

Table 4. NIH quality assessment and risk of bias of included studies.

	Research question clearly stated	Study population clearly defined	Uniform subject selection	Sample size justification	Exposure measured prior to the outcome	Timeframe between exposure and outcome	Exposure measurement	Exposure definition	Outcome measurement	Loss to follow-up after baseline 20% or less	Adjusted for tumor stage and liver dysfunction
Kanwal et al., 2012[40]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Wong et al., 2012[41]	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	NR	No
Davila et al., 2013[31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	No
Singal et al., 2013[28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Wong et al., 2014[42]	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	NR	No
Hoehn et al., 2015[43]	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	NR	No
Chidi et al., 2016[12]	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	NR	No
Sarpel et al., 2016[11]	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	No

Table 4. Continued.

	Research question clearly stated	Study population clearly defined	Uniform subject selection	Sample size justification	Exposure measured prior to the outcome	Timeframe between exposure and outcome	Exposure measurement	Exposure definition	Outcome measurement	Loss to follow-up after baseline 20% or less	Adjusted for tumor stage and liver dysfunction
Stewart et al., 2016[10]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	No
Kokabi et al., 2017[44]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	No
Dakhoul et al., 2019[45]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes
Rich et al., 2019[8]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes
Scaglione et al., 2020[9]	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	NR	No

2.5. Discussion

Our study extends the current published literature by characterizing and quantifying racial-ethnic disparities in receiving HCC-specific treatment. Additionally, we also summarized factors like SES, insurance, and geographic factors that can have additive effects on these existing disparities. We demonstrated statistically significant disparities between Black and White patients in receiving curative and any (curative and non-curative) treatment. Moreover, Hispanic patients had lower odds of receipt of curative treatment when compared to White patients. There were no statistically significant disparities between Asian and White patients receiving curative treatment. Prior studies have demonstrated lower odds of treatment associated with worse survival among Black and Hispanic patients.[9,11,12,21,42] However, these studies do not explore this interplay between race, ethnicity, and SDOH among HCC patients. Understanding the interplay between race, ethnicity, and SDOH in HCC treatment remains critical as we identify interventions that target specific populations at a higher risk of not receiving care.

Furthermore, issues within the patient-provider relationship have been known to affect treatment course and subsequent outcomes in cancer patients.[46] Furthermore, a patient's cultural background can invoke implicit bias and affect the course of their care.[47–50] Future studies should seek to understand how cultural barriers and provider bias affect receipt of HCC treatment among traditionally marginalized communities in the US.

Lower access to care among racial-ethnic minorities may not entirely explain disparities in receipt of treatment. For example, Hispanic patients are known to have a higher burden of HCV, whereas Asian patients are known to have a higher HBV burden when compared to White patients.[3] Additionally, Black patients may develop HCC much earlier, thus not being captured through current HCC screening guidelines.[51] Hence, clinical factors like ECOG performance status, MELD score, Child-Pugh Class, and liver disease etiology are critical to examining treatment receipt among HCC patients. Studies in this meta-analysis which used cancer registries to evaluate receipt of HCC-specific treatment, often did not have information on performance status, MELD score, Milan criteria, and advanced liver disease predictors.[10,12,42–44] Future studies could link data with claims information to capture treatment information beyond the first course, clinical predictors like liver disease etiology, and advanced liver disease predictors. However, even after the linkage, most population-based datasets may not be able to adjust for critical clinical factors like ECOG performance status, MELD score, Child-Pugh class, and laboratory values for indicators like albumin, bilirubin, and platelet count.

This meta-analysis is not without limitations. Since we included only peer-reviewed articles in our meta-analysis, publication bias cannot be overlooked. Since our meta-analysis included only 13 studies, we did not have sufficient data to calculate the pooled OR estimate of any treatment receipt for Asian and Hispanic patients. Additionally, we had insufficient data for accounting for disparities between Native American and White patients due to deficient information on Native American patients

in the included studies. More focus needs to be on obtaining data on racial-ethnic groups like Native Americans and multiracial groups. Our study results should be interpreted with caution due to heterogeneity between different ethnicities within racial-ethnic groups like Blacks, Asians, and Hispanics.

In conclusion, there are significant racial and ethnic disparities in receipt of curative treatment among patients with HCC in the US. However, none of the studies examine the intersectionality of race/ethnicity and SDOH on receipt of curative treatment. Future studies should be designed to explore this intersectionality to further understand these disparities and design interventions that seek to reduce these disparities. Such interventions would be crucial to achieving equitable outcomes among traditionally marginalized populations in the United States.

3. RACIAL, ETHNIC, AND SOCIOECONOMIC DISPARITIES IN CURATIVE TREATMENT RECEIPT AND SURVIVAL IN HEPATOCELLULAR CARCINOMA*[1]

3.1. Introduction

Hepatocellular carcinoma (HCC) results in over 700,000 deaths globally every year, and it is one of the fastest rising causes of cancer-related mortality in the United States. [3] The five-year survival for HCC remains below 20%. Prognosis markedly differs by tumor stage at diagnosis. [52] Patients with early-stage HCC are eligible for curative surgical therapy, such as resection or liver transplantation, and can achieve five-year survival rates exceeding 60%. [1] Conversely, median survival is typically one to two years for those with a more advanced tumor burden. [5]

HCC disproportionately affects racial and ethnic minorities and low socioeconomic status (SES) populations, with significantly higher HCC incidence and mortality rates in Black and Hispanic patients than non-Hispanic Whites. [5–7] However, fewer studies examine racial/ethnic and socioeconomic disparities in HCC prognosis, including overall survival. A prior systematic review found curative treatment is often underused in clinical practice, with only 22% of all HCC patients and 59% of patients with early-stage HCC undergoing curative treatment. [20] However, only five studies in

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*[1]Reprinted with permission from Wagle NS, Park S, Washburn D, et al. Racial, Ethnic, and Socioeconomic Disparities in Curative Treatment Receipt and Survival in Hepatocellular Carcinoma. Hepatol Commun. n/a(n/a). doi:10.1002/hep4.1863,

this systematic review described racial, ethnic, or socioeconomic disparities in treatment receipt. [20] Similarly, a recent systematic review found Black patients with HCC had lower odds of early tumor detection and worse overall survival than non-Hispanic whites, although the study did not directly address the interaction between race-ethnicity and SES. Although race, ethnicity, and SES are interrelated, they may impact health outcomes distinctly and have additive contributions to observed health disparities. Studies in other cancer types, including lung, ovarian, breast, prostate, and colorectal cancer, have shown that lower neighborhood SES is independently associated with worse survival. [22–26] However, there are few if any data examining the interaction between race, ethnicity, and neighborhood SES in patients with HCC. [8]

Therefore, we performed a retrospective cohort study to characterize the interaction of racial, ethnic, and neighborhood socioeconomic disparities in curative treatment utilization and overall survival in the United States among a large population-based sample of patients with HCC.

3.2. Methods

3.2.1. Data sources

We performed a retrospective cohort study using the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER)-Medicare data between the years of 2001 to 2015. SEER is an epidemiological surveillance program that collects data on incident cancer cases from population-based cancer registries, covering 34.6% of the U.S. [53] The linked SEER-Medicare database combines these two population-based databases providing information on diagnosis, survival, demographics, and health

services utilization of cancer patients from Medicare eligibility until death. [54] This study protocol was reviewed and deemed not human subjects research by the Institutional Review Board at Texas A&M University.

3.2.2. Study population

We included all Medicare beneficiaries aged 65 years and older who were diagnosed with HCC (International Classification of Diseases for Oncology, Third edition, [ICD] - [O] histology code 8170 and site code C22.0 for liver) between 2001 and 2015. [55] Only patients with diagnostically confirmed HCC (positive histology, cytology, laboratory test, positive radiology tests) were included. We excluded patients who: (1) were not continuously enrolled in Medicare Part A and B, one year prior and post HCC diagnosis; (2) were enrolled in health maintenance organizations (HMOs); [54,56] (3) had missing characteristics that could not be imputed; [56] (4) died within 30 days post HCC diagnosis; or (4) were diagnosed with other cancers one year prior to HCC diagnosis. (**Supplemental Figure 1**, Appendix B**)**

3.2.3. Study variables

3.2.3.1. Outcomes

The primary outcome of interest was the receipt of curative treatment. Curative treatment was defined as liver transplantation, surgical resection, or local ablation, and identified from Medicare data using the International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-9 and ICD-10-PCS), and Current Procedure Terminology (CPT) codes within 12 months post HCC diagnosis. [31] Our secondary

outcome was overall survival, defined as the time from HCC diagnosis (in months) to the date of death from any cause.

3.2.3.2. Neighborhood-level Socioeconomic status

Census tract poverty level (CPL) was abstracted from the SEER Patient Entitlement and Diagnosis Summary File (PEDSF) and used as a proxy for neighborhood-level socioeconomic status (SES), defined as the proportion of the population living in poverty in the patient's residential census tract at the time of HCC diagnosis. We used 2000 U.S. Census tract data for diagnosis years 2000 – 2005 and 2010 U.S. Census tract data for diagnosis years 2006 – 2015 and categorized CPL for each patient as follows: high poverty (20% to 100% poverty), moderate poverty neighborhoods (10% to less than 20% poverty), and low poverty neighborhoods (0% to less than 10% poverty), as previously described in the literature. [26,57,58]

3.2.3.3. Race, ethnicity, and other sociodemographic characteristics

SEER PEDSF was used to abstract information on race and ethnicity, age, sex, geographic region (Northeast, West, Midwest, and South), year of diagnosis, and census tract-level educational attainment. Race and ethnicity variable was categorized as non-Hispanic White (White), non-Hispanic Black (Black), Hispanic, Asian/Pacific Islander (Asian), and "other/unknown." Educational attainment was defined as the proportion of the population, 25 years or older, with at least 12 years of education.

3.2.3.4. Clinical characteristics

Liver disease etiology was identified using Medicare data and was hierarchically categorized as hepatitis C virus (HCV), hepatitis B virus (HBV), alcohol-related liver

disease, other liver diseases (hemochromatosis, disorders of copper metabolism, porphyria), metabolic associated fatty liver disease (MAFLD) and no identifiable liver diseases. The severity of liver dysfunction was assessed by the presence of ascites (ICD-9: 789.51, 789.59 and ICD-10 code R18.0, R18.8) or hepatic encephalopathy (ICD-9: 572.2 and ICD-10 code K72.90, K72.91) at least 12 months before HCC diagnosis using Medicare claims. We used diagnosis and procedure codes in the year preceding HCC diagnosis to calculate the National Cancer Institute (NCI) Comorbidity Index as a measure of non-cancer comorbidity. [59,60] Receipt of abdominal ultrasound within one year prior to HCC diagnosis was captured as a proxy for screening from outpatient and physician/supplier claims data. Early-stage HCC patients were defined as patients with unifocal lesion <=5 cm with no evidence of vascular invasion or distant metastases. We conducted a sensitivity analysis using SEER stage, classified as localized, regional, or distant.

3.2.4. Statistical analysis

Chi-square tests were used to compare characteristics of the study population by receipt of curative treatment. Multivariable logistic regression with time fixed effects was performed to examine the impact of race and ethnicity on receipt of curative treatment across socioeconomic strata. We calculated robust standard errors to account for clustering at the census tract level. Survival time was measured in months from HCC diagnosis to death from any cause. People who were alive on December 31, 2017, were censored on that date. We estimated overall survival by race, ethnicity across the socioeconomic strata using Kaplan-Meier analysis. Log-rank tests were used to compare

survival distributions by race, ethnicity, and SES. We then performed univariable and multivariable Cox proportional hazards analyses for each SES subgroup to examine the association between race, ethnicity, and survival across socioeconomic strata. We reported the associations from our multivariable models as adjusted odds ratios (OR) and adjusted hazard ratios (HR) with 95% confidence intervals (CI). All P values were two-sided with a statistical significance p less than 0.05. We conducted a subgroup analysis among patients with early-stage HCC. All statistical analyses were performed using Stata version 16.1 (StataCorp, College Station, TX).

3.3. Results

A total of 46,998 patients were diagnosed with HCC between 2001 and 2015 (**Figure 1**). We excluded 25,084 patients (12.1% Black, 5.8% Hispanic) due to lack of continuous enrollment in Medicare Part A and B or enrollment in HMOs, 4,563 patients with missing sociodemographic information, 2,901 patients who died within 30 days post HCC diagnosis (11.3% Black, 4.6% Hispanic), and 486 patients with other cancers one year prior to HCC diagnosis. There were 13,874 patients with HCC who remained eligible for inclusion in the final sample set (**Supplemental Figure 1**, Appendix B).

Baseline patient characteristics are detailed in **Table 5.**

Table 5. Characteristics of patients diagnosed with HCC (2001 – 2015).

	Overall (n=13874) n (%)		Early-stage HCC[2] (n=2457) n (%)	
Curative treatment				
Not received	11257	81.1%	1546	62.9%
Received	2617	18.9%	911	37.1%
Age at diagnosis				
65 years – 69 years	3438	24.8%	757	30.8%
70 years – 74 years	3665	26.4%	677	27.6%
75 years – 79 years	3244	23.4%	523	21.3%
80 years and over	3527	25.4%	500	20.4%
Gender				
Female	4442	32.0%	944	38.4%
Male	9432	68.0%	1513	61.6%
Race and ethnicity				
White	9594	69.2%	1593	64.8%
Black	1161	8.4%	189	7.7%
Asian	1675	12.1%	356	14.5%
Hispanic	573	4.1%	116	4.7%
Other/Unknown	871	6.3%	203	8.3%
Neighborhood-level SES				
Affluent neighborhoods	6489	46.8%	1092	44.4%
Moderate poverty neighborhoods	4145	29.9%	765	31.1%
Poor neighborhoods	3240	23.4%	600	24.4%
Census tract education level (mean, standard deviation)	17.7	13.6	17.2	13.5
Geographic region				
Northeast	2469	17.8%	319	13.0%
West	7377	53.2%	1497	60.9%
Midwest	1334	9.6%	222	9.0%
South	2694	19.4%	419	17.1%
Abdominal Ultrasound				
No	8463	61.0%	1165	46.4%
Yes	5411	39.0%	1292	52.6%
Unifocal lesion				
No	6603	47.6%		
Yes	2457	17.7%	N/A	N/A
Non-determinable	4814	34.7%		

Table 5. Continued.

[2] Early-stage HCC was defined using the unifocal lesion ≤5 cm without vascular invasion or metastatic spread.

	Overall (n=13874) n (%)		Early-stage HCC (n=2457) n (%)	
SEER Stage				
Localized	7290	52.5%		
Regional	3592	25.9%	N/A	N/A
Distant	1764	12.7%		
Unknown	1228	8.9%		
NCI comorbidity index				
0	3186	23.0%	457	18.6%
1	2974	21.4%	453	18.4%
2	2372	17.1%	681	27.7%
3	2312	16.7%	684	27.8%
4	831	6.0%	210	8.5%
>=5	2199	15.8%	576	23.4%
Liver disease etiology				
No identifiable liver disease	2885	20.8%	281	11.4%
HCV	3589	25.9%	979	39.8%
HBV	587	4.2%	176	7.2%
Alcohol related liver disease	1379	9.9%	302	12.3%
Other liver disease[3]	244	1.8%	51	2.1%
MAFLD[4]	5190	37.4%	668	27.2%
Liver dysfunction				
Presence of hepatic encephalopathy	815	5.9%	265	10.8%
Presence of ascites	1481	10.7%	457	18.6%
Year of diagnosis				
2001	627	4.5%	62	2.5%
2002	735	5.3%	75	3.1%
2003	694	5.0%	85	3.5%
2004	807	5.8%	124	5.0%
2005	802	5.8%	99	4.0%
2006	783	5.6%	132	5.4%
2007	881	6.4%	139	5.7%
2008	918	6.6%	161	6.6%
2009	953	6.9%	166	6.8%
2010	998	7.2%	209	8.5%
2011	1068	7.7%	195	7.9%
2012	1111	8.0%	224	9.1%
2013	1154	8.3%	242	9.8%
2014	1146	8.3%	253	10.3%
2015	1197	8.6%	291	11.8%

[3] Other liver diseases include hemochromatosis, disorders of copper metabolism, porphyria.

[4] Metabolic Associated Fatty Liver Disease

The median age was 75 years, and over two-thirds (68.0%) of patients were male. The cohort was racially diverse (69.1% Whites, 8.4% Blacks, 12.1% Asians, and 4.1% Hispanics) and had socioeconomic diversity, with 46.8% of patients residing in low poverty neighborhoods, 29.9% in moderate poverty neighborhoods, and 23.3% in high poverty neighborhoods. Most (61.0%) patients did not receive ultrasound-based screening within one year prior to HCC diagnosis, although screening was higher (52.6%) among those with early-stage HCC. Blacks had lower receipt of ultrasound in year prior to HCC diagnosis than Whites and Hispanics (33.8% vs 36.7% and 46.9%, respectively). Although more than half (52.5%) of the patients had localized SEER stage, only one-fifth (17.7%) were detected with a unifocal HCC ≤5 cm without vascular invasion or distant metastases.

3.3.1. Receipt of curative treatment

A minority of patients received curative treatment, including 2,617 (18.9%) of the entire cohort of patients. Of the 2,617 who received curative treatment, 68.0% were White, 7.2% were Black, 13.3% were Asian, and 3.3% were Hispanic (**Supplemental Table 1**, Appendix B). Of the 2,457 patients with early-stage HCC, 911 (37.1%) received curative treatment and among those who received curative treatment, 62.9% were white, 7.8% were Black, 15.1% were Asian, and 4.2% were Hispanic.

In multivariable analyses (**Table 6**), men, older patients, and those with higher comorbidity had lower odds of curative treatment receipt.

Table 6. Odds of curative treatment receipt among patients with HCC.

	Base Model n=13874 OR (95% CI)	Low poverty Neighborhoods n=6489 OR (95% CI)	Moderate Poverty Neighborhoods n=4145 OR (95% CI)	High poverty Neighborhoods n=3240 OR (95% CI)
Age at diagnosis				
65 years – 69 years	Ref	Ref	Ref	Ref
70 years – 74 years	0.88 (0.78,0.99)	0.82 (0.69,0.97)	0.99 (0.78,1.24)	0.91 (0.72,1.17)
75 years – 79 years	0.67 (0.59,0.76)	0.62 (0.52,0.74)	0.75 (0.59,0.960	0.71 (0.54,0.93)
80 years and over	0.44 (0.38,0.51)	0.40 (0.33,0.49)	0.53 (0.41,0.68)	0.41 (0.30,0.56)
Male	0.82 (0.74,0.91)	0.82 (0.71,0.95)	0.97 (0.81,1.17)	0.68 (0.55,0.84)
Race and ethnicity				
White	Ref	Ref	Ref	Ref
Black	0.76 (0.64,0.91)	0.80 (0.56,1.14)	0.89 (0.64,1.23)	0.64 (0.49,0.84)
Asian	1.04 (0.90,1.21)	1.01 (0.81,1.26)	1.22 (0.92,1.62)	0.95 (0.68,1.31)
Hispanic	0.92 (0.72,1.17)	0.73 (0.43,1.24)	0.64 (0.39,1.04)	1.29 (0.89,1.87)
Other/Unknown	1.19 (1.00,1.42)	1.30 (1.02,1.64)	1.23 (0.88,1.73)	0.93 (0.59,1.45)
Neighborhood-level SES		–	–	–
Low poverty neighborhoods	Ref			
Moderate poverty neighborhoods	0.89 (0.79,1.00)			
High poverty neighborhoods	1.03 (0.89,1.20)			

Table 6. Continued.

	Base Model n=13874 OR (95% CI)	Low poverty Neighborhoods n=6489 OR (95% CI)	Moderate Poverty Neighborhoods n=4145 OR (95% CI)	High poverty Neighborhoods n=3240 OR (95% CI)
Census tract education level	0.99 (0.98,0.99)	0.98 (0.97,0.99)	0.99 (0.98,1.00)	0.99 (0.98,1.00)
Geographic region				
West	Ref	Ref	Ref	Ref
Northeast	1.46 (1.28,1.66)	1.34 (1.15,1.57)	1.66 (1.25,2.19)	1.83 (1.25,2.67)
Midwest	1.10 (0.93,1.30)	1.00 (0.80,1.26)	1.23 (0.90,1.67)	1.33 (0.93,1.91)
South	1.21 (1.07,1.38)	1.17 (0.95,1.43)	1.30 (1.04,1.61)	1.27 (0.97,1.65)
Unifocal lesion				
No	Ref	Ref	Ref	Ref
Yes	2.64 (2.37,2.94)	2.34 (1.99,2.75)	2.96 (2.40,3.65)	2.94 (2.37,3.65)
Non-determinable	0.66 (0.59,0.73)	0.65 (0.56,0.76)	0.71 (0.57,0.88)	0.61 (0.47,0.78)
NCI comorbidity index				
0	Ref	Ref	Ref	Ref
1	0.95 (0.82,1.11)	0.87 (0.71,1.06)	0.95 (0.73,1.25)	1.21 (0.90,1.63)
2	1.02 (0.88,1.18)	1.00 (0.82,1.22)	1.05 (0.79,1.38)	1.04 (0.76,1.42)
3	1.00 (0.86,1.16)	0.95 (0.78,1.17)	0.96 (0.73,1.28)	1.20 (0.87,1.66)
4	0.90 (0.73,1.11)	0.85 (0.63,1.14)	1.05 (0.72,1.52)	0.85 (0.51,1.41)
>=5	0.62 (0.53,0.73)	0.63 (0.50,0.79)	0.57 (0.41,0.77)	0.69 (0.49,0.95)

Table 6. Continued.

	Base Model n=13874 OR (95% CI)	Low poverty Neighborhoods n=6489 OR (95% CI)	Moderate Poverty Neighborhoods n=4145 OR (95% CI)	High poverty Neighborhoods n=3240 OR (95% CI)
Liver disease etiology				
HCV	Ref	Ref	Ref	Ref
HBV	1.32 (1.07,1.64)	1.18 (0.88,1.59)	1.52 (1.01,2.28)	1.45 (0.90,2.35)
Alcohol related liver disease	0.61 (0.51,0.72)	0.69 (0.54,0.88)	0.61 (0.44,0.86)	0.42 (0.28,0.63)
Other liver disease	0.98 (0.72,1.33)	1.21 (0.81,1.80)	0.96 (0.53,1.75)	0.41 (0.17,0.98)
MAFLD	0.75 (0.66,0.84)	0.76 (0.64,0.91)	0.81 (0.65,1.01)	0.66 (0.52,0.85)
No identifiable liver disease	0.57 (0.49,0.65)	0.64 (0.52,0.79)	0.48 (0.36,0.65)	0.49 (0.36,0.68)
Liver dysfunction				
Presence of hepatic encephalopathy	0.87 (0.71,1.06)	0.82 (0.62,1.10)	0.93 (0.64,1.35)	0.94 (0.62,1.43)
Presence of ascites	1.00 (0.85,1.17)	1.04 (0.82,1.30)	1.20 (0.89,1.61)	0.74 (0.53,1.03)

Table 6. Continued.

	Base Model n=13874 OR (95% CI)	Low poverty Neighborhoods n=6489 OR (95% CI)	Moderate Poverty Neighborhoods n=4145 OR (95% CI)	High poverty Neighborhoods n=3240 OR (95% CI)
Year of diagnosis				
2001	Ref	Ref	Ref	Ref
2002	1.19 (0.87,1.64)	1.33 (0.87,2.05)	1.30 (0.72,2.36)	0.78 (0.37,1.64)
2003	1.15 (0.83,1.60)	1.13 (0.73,1.74)	1.01 (0.53,1.92)	1.52 (0.76,3.04)
2004	1.05 (0.78,1.43)	0.92 (0.61,1.40)	1.26 (0.70,2.27)	1.34 (0.67,2.68)
2005	1.14 (0.84,1.55)	1.02 (0.66,1.56)	1.11 (0.61,2.02)	1.60 (0.84,3.04)
2006	0.99 (0.73,1.35)	1.10 (0.73,1.66)	0.84 (0.45,1.56)	0.97 (0.48,1.97)
2007	1.00 (0.74,1.34)	1.02 (0.68,1.54)	0.93 (0.52,1.66)	1.03 (0.54,1.99)
2008	1.02 (0.76,1.38)	1.18 (0.79,1.77)	1.00 (0.57,1.76)	0.62 (0.30,1.27)
2009	0.95 (0.71,1.28)	0.96 (0.64,1.46)	0.73 (0.41,1.31)	1.29 (0.67,2.46)
2010	0.90 (0.67,1.21)	0.99 (0.65,1.50)	0.77 (0.44,1.36)	0.87 (0.46,1.63)
2011	0.96 (0.71,1.30)	1.00 (0.66,1.52)	0.89 (0.50,1.58)	1.00 (0.53,1.86)
2012	0.90 (0.67,1.20)	0.95 (0.62,1.44)	0.74 (0.42,1.32)	1.06 (0.58,1.93)
2013	1.03 (0.77,1.37)	1.03 (0.68,1.56)	0.90 (0.51,1.58)	1.17 (0.63,2.16)
2014	0.86 (0.64,1.16)	0.86 (0.57,1.29)	0.70 (0.39,1.26)	1.08 (0.57,2.05)
2015	1.05 (0.79,1.41)	1.00 (0.67,1.50)	0.90 (0.51,1.60)	1.38 (0.74,2.55)

Geographic differences were also observed, with patients living in Northeastern and Southern regions having higher odds of curative treatment than those in the West. We observed significant racial disparities, with Black patients having lower odds of receiving curative treatment (OR 0.76, 95%CI 0.64 - 0.91) compared to White patients. Patients in moderate poverty neighborhoods also had lower odds of receiving treatment (OR 0.89 95%CI 0.79 - 1.00) when compared to patients living in low poverty neighborhoods. When stratified by SES, Black patients in high poverty neighborhoods

continued to have lower odds of curative treatment compared to Whites (OR 0.64, 95%CI 0.49 - 0.84); however, there were no significant differences in curative treatment receipt between Black and White patients living in low poverty (OR 0.80, 95%CI 0.54 - 1.14) or moderate poverty (OR 0.89, 95%CI 0.64 - 1.23) neighborhoods. No significant disparities in curative treatment receipt were observed for Hispanic and Asian patients in comparison to White patients, irrespective of neighborhood SES.

As expected, patients with early-stage HCC had 2.64 times higher odds (95%CI 2.37 - 2.94) of receiving curative treatment than patients presenting with larger tumor burden. Among early-stage HCC patients, older age, higher comorbidity index, and alcohol-related liver disease had lower odds of curative treatment receipt (**Supplemental Table 2**, Appendix B). We did not observe significant racial and socioeconomic disparities between Black and White patients irrespective of the socioeconomic status. However, we observed Hispanics in high poverty neighborhoods had higher odds of receiving curative treatment when compared to White patients (OR 1.92, 95%CI 1.03 - 3.56). In contrast, there were no significant differences in curative treatment receipt between Hispanic and White patients living in low poverty (OR 0.58, 95%CI 0.22 - 1.56) or moderate poverty (OR 0.73, 95%CI 0.34 - 1.55) neighborhoods.

3.3.2. Overall Survival

Median survival for the entire cohort was 11 (IQR 4 to 33) months. Median survival was 10, 9, 17, and 10 months for White, Black, Asian, and Hispanic patients, respectively. Overall unadjusted survival, stratified by race, ethnicity, and SES, for the cohort is illustrated in **Figure 9** and **Figure 10**.

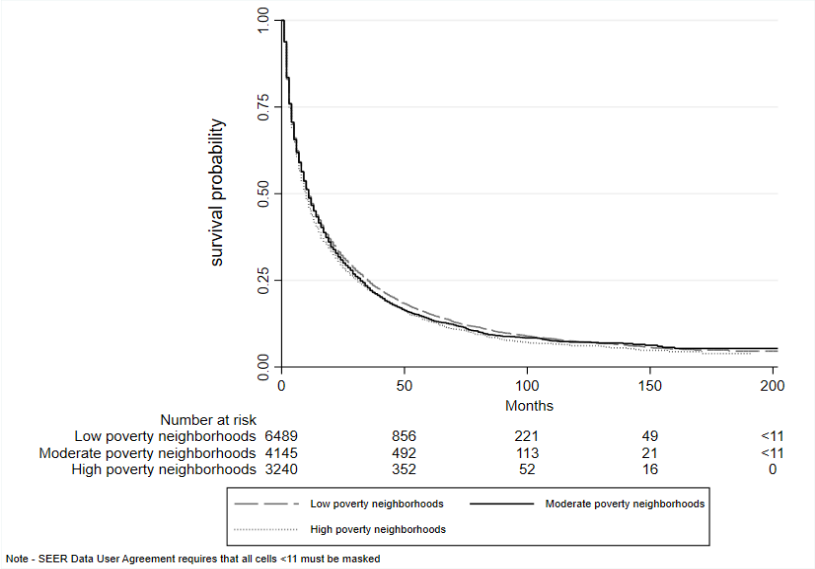

Figure 9. Overall unadjusted survival stratified by neighborhood SES level

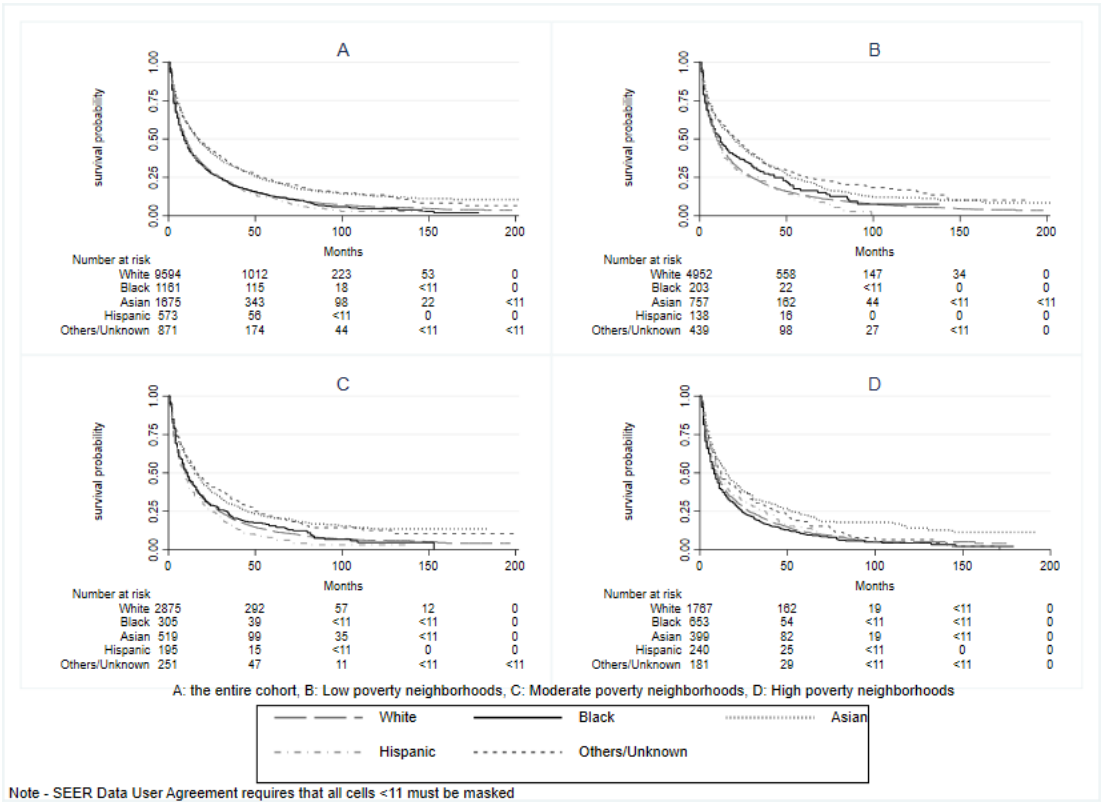

Figure 10. Overall unadjusted survival stratified by race for the overall cohort and at each neighborhood SES level.

Multivariable Cox proportional hazards model identified several sociodemographic and clinical predictors of overall survival (**Table 7**).

Table 7. Predictors of overall survival.

	Base Model n=13874 HR (95% CI)	Low poverty Neighborhoods n=6489 HR (95% CI)	Moderate Poverty Neighborhoods n=4145 HR (95% CI)	High poverty Neighborhoods n=3240 HR (95% CI)
Curative treatment				
Not received	Ref	Ref	Ref	Ref
Received	0.42 (0.40,0.44)	0.43 (0.40,0.46)	0.41 (0.37,0.45)	0.42 (0.38,0.46)
Age at diagnosis				
65 years – 69 years	Ref	Ref	Ref	Ref
70 years – 74 years	1.12 (1.06,1.18)	1.14 (1.05,1.23)	1.12 (1.01,1.23)	1.10(1.00,1.22)
75 years – 79 years	1.22 (1.15,1.29)	1.30 (1.20,1.41)	1.15 (1.04,1.27)	1.17 (1.04,1.30)
80 years and over	1.32 (1.25,1.39)	1.44 (1.33,1.56)	1.27 (1.16,1.40)	1.19 (1.06,1.33)
Male	1.03 (0.99,1.07)	1.04 (0.98,1.10)	1.00 (0.93,1.07)	1.07 (0.98,1.16)
Race and ethnicity				
White	Ref	Ref	Ref	Ref
Black	1.01 (0.94,1.08)	0.87 (0.73,1.04)	0.95 (0.82,1.09)	1.13 (1.02,1.25)
Asian	0.79 (0.74,0.84)	0.76 (0.69,0.83)	0.88 (0.78,0.98)	0.75 (0.65,0.86)
Hispanic	0.97 (0.88,1.06)	0.97 (0.82,1.15)	1.06 (0.92,1.23)	0.92 (0.78,1.07)
Other/Unknown	0.83 (0.77,0.90)	0.80 (0.71,0.90)	0.83 (0.71,0.97)	0.91 (0.78,1.06)

Table 7. Continued.

	Base Model n=13874 HR (95% CI)	Low poverty Neighborhoods n=6489 HR (95% CI)	Moderate Poverty Neighborhoods n=4145 HR (95% CI)	High poverty Neighborhoods n=3240 HR (95% CI)
Neighborhood-level SES		–	–	–
Low poverty neighborhoods	Ref			
Moderate poverty neighborhoods	0.97 (0.92,1.01)			
High poverty neighborhoods	0.95 (0.89,1.01)			
Census tract education level	1.00 (1.00,1.01)	1.01 (1.00,1.01)	1.01 (1.00,1.01)	1.00 (1.00,1.01)
Geographic region				
West	Ref	Ref	Ref	Ref
Northeast	0.97 (0.92,1.02)	0.96 (0.90,1.03)	1.00 (0.90,1.12)	0.88 (0.76,1.03)
Midwest	1.12 (1.04,1.19)	1.17 (1.06,1.29)	1.09 (0.97,1.22)	0.97 (0.84,1.11)
South	1.11 (1.05,1.17)	1.10 (1.00,1.20)	1.07 (0.98,1.16)	1.12 (1.02,1.23)
Unifocal lesion				
No	Ref	Ref	Ref	Ref
Yes	0.57 (0.54,0.60)	0.55 (0.51,0.60)	0.56 (0.51,0.62)	0.58 (0.53,0.64)
Non-determinable	1.14 (1.10,1.19)	1.16 (1.09,1.23)	1.14 (1.05,1.22)	1.12 (1.03,1.21)

Table 7. Continued.

	Base Model n=13874 HR (95% CI)	Low poverty Neighborhoods n=6489 HR (95% CI)	Moderate Poverty Neighborhoods n=4145 HR (95% CI)	High poverty Neighborhoods n=3240 HR (95% CI)
NCI comorbidity index				
0	Ref	Ref	Ref	Ref
1	1.01 (0.96,1.07)	1.00 (0.92,1.09)	1.01 (0.91,1.11)	1.04 (0.92,1.17)
2	0.93 (0.88,0.99)	1.00 (0.91,1.09)	0.89 (0.79,1.00)	0.86 (0.76,0.98)
3	0.94 (0.88,1.00)	1.01 (0.91,1.11)	0.86 (0.77,0.97)	0.91 (0.80,1.03)
4	1.16 (1.07,1.26)	1.21 (1.08,1.37)	1.30 (1.12,1.52)	0.92 (0.78,1.09)
>=5	1.13 (1.07,1.21)	1.23 (1.12,1.36)	1.15 (1.03,1.28)	0.96 (0.85,1.08)
Liver disease etiology				
HCV	Ref	Ref	Ref	Ref
HBV	1.25 (1.18,1.32)	1.21 (1.11,1.32)	1.32 (1.18,1.46)	1.27 (1.13,1.43)
Alcohol related liver disease	0.84 (0.75,0.93)	0.86 (0.74,1.01)	0.78 (0.64,0.94)	0.86 (0.68,1.08)
Other liver disease	1.14 (1.06,1.22)	1.11 (1.00,1.22)	1.22 (1.07,1.39)	1.13 (0.98,1.32)
MAFLD	0.97 (0.85,1.11)	1.00 (0.82,1.20)	1.06 (0.83,1.36)	0.70 (0.47,1.02)
No identifiable liver disease	1.22 (1.16,1.28)	1.22 (1.13,1.31)	1.19 (1.08,1.30)	1.28 (1.15,1.41)
Liver dysfunction				
Presence of hepatic encephalopathy	0.97 (0.89,1.07)	1.04 (0.91,1.19)	0.89 (0.77,1.04)	0.96 (0.81,1.14)
Presence of ascites	1.20 (1.12,1.28)	1.19 (1.07,1.33)	1.22 (1.08,1.37)	1.22 (1.07,1.40)

Older patients (age > 70 years), those living in the Midwest and South, those with higher comorbidity, and patients with ascites had worse survival than their

counterparts. As expected, early-stage HCC detection (HR 0.57, 95%CI 0.54 - 0.60) and curative treatment receipt (HR 0.42, 95%CI 0.40 - 0.44) were both associated with improved survival.

We observed racial, ethnic, and socioeconomic disparities in overall survival. Black patients in poor neighborhoods had worse survival than White patients (HR 1.13, 95%CI 1.02 - 1.25). In contrast, we found no significant Black-White disparities in survival in moderate poverty (HR 0.95 95% CI 0.82 -1.09) or low poverty (HR 0.87 95% CI 0.73 -1.04) neighborhoods. Asian patients had lower mortality than White patients irrespective of SES (low poverty neighborhoods: HR 0.76, 95%CI 0.69 - 0.83; moderate poverty neighborhoods HR 0.88, 95%CI 0.78 - 0.98; high poverty neighborhoods: HR 0.75, 95%CI 0.65 - 0.86). No significant disparities in overall survival were observed between Hispanic and White patients, irrespective of SES. Among those with early-stage HCC, Asian-White disparities persisted across SES strata; however, we found no significant disparities between White and Black or Hispanic patients irrespective of SES (**Supplemental Table 3**, Appendix B).

3.4. Discussion

In this analysis of the SEER-Medicare database, we found that less than one-fifth of patients with HCC received curative treatment, including less than one-third of those with early-stage HCC, leading to a poor median overall survival of only eleven months. Further, we observed statistically significant racial, ethnic and neighborhood socioeconomic disparities in receipt of curative treatment for HCC. Black patients were significantly less likely to undergo curative treatment and have worse overall survival

than Whites, whereas we did not observe Hispanic-White disparities in curative treatment receipt or overall survival. Notably, disparities in curative treatment receipt were less marked among those with early-stage HCC than all patients, suggesting observed disparities were in part driven by differences in tumor burden at diagnosis. The striking Black-White disparities in HCC prognosis identified in our study are consistent with prior studies and parallel the conclusions from a recent systematic review. [20] Our study extends the prior literature by examining the intersection of race, ethnicity, and SES in HCC prognosis in a large population-based patient sample. Notably, despite the study cohort representing an insured population of Medicare enrollees, we found Black-White disparities in treatment and survival appear to be moderated by SES, as we observed these disparities only in poor neighborhoods and not in moderate poverty or low poverty neighborhoods. These data provide further context in our understanding of the interplay between racial, ethnic, and neighborhood socioeconomic disparities in HCC prognosis; this is critical as we move from a model of simply describing health disparities to understanding why disparities exist and developing interventions to promote health equity.

The root causes of HCC curative treatment disparities are complex and likely related to a combination of factors at the individual (e.g., misconceptions about cancer treatment, mistrust, transportation barriers, caregiver burden), provider (e.g., implicit and/or explicit biases), and system (e.g., hospital volume and facilities) levels. [61] Furthermore, all these factors may be intertwined with and exacerbated by individual and neighborhood-level poverty and inextricably linked to healthcare access. Our study

also highlights that simply having health insurance does not remove all barriers, as disparities in guideline-concordant HCC care exist even among those with equal health coverage (in this case, Medicare enrollees). [62–64] Further, insured patients with limited financial means may still have difficulty affording out-of-pocket costs for medications and clinic visits. Patients living in poor neighborhoods may also have other non-insurance-related barriers that can result in missed visits and postponed care or shortages of physicians and subspecialists in medically underserved areas. [27,65–67] In particular, the availability of liver transplantation and hepatic resection may be limited in these areas. [68] Differential access to healthcare may not wholly explain racial and ethnic disparities in prognosis and subsequent receipt of curative treatment. For instance, there is increasing evidence highlighting the role of epigenetic effects and chronic stress from racism and poverty, leading to immunologic changes that may impact cancer biology and prognosis. [69,70] Several studies have suggested lower HCC surveillance receipt in racial-ethnic minorities and more advanced tumor burden at diagnosis. [8,27,62,66] Although recent data suggest variation in tumor growth patterns, there are no ethnic disparities in the frequency of common somatic mutations associated with HCC (e.g., CTNNB1) and no convincing data demonstrating racial, ethnic disparities in tumor biology and growth patterns. [69,70] Compared to other racial-ethnic groups, Asians are more likely to have underlying HBV infection, which can cause HCC in the absence of cirrhosis and may facilitate curative surgical resection. Recent data suggest Black patients may develop HCC at earlier stages of fibrosis, outside of traditional surveillance criteria, which may be one of the reasons they present at more advanced HCC stages. [51] Although our study

highlights the complexity of racial and ethnic disparities, particularly the intersection with race-ethnicity and SES, further studies are needed to evaluate these sociodemographic disparities' mediating pathways.

Strengths of our study include a large population-based patient sample and novel analysis characterizing the interaction between race, ethnicity and neighborhood socioeconomic status and its impact on curative treatment utilization and survival. Further, linkage to the Medicare database provided us with some clinical information not included in SEER (e.g., liver disease etiology, ascites/encephalopathy), more detailed treatment data, and an improvement over using one or the other data alone. We acknowledge that our study also has limitations. Our analysis included older patients, limiting generalizability to younger patients, who may be more likely to undergo curative therapies. [71] Though SEER is an extensive population-based data; it does not include all geographic regions in the U.S., limiting generalizability given the geographic variation in HCC treatment receipt and prognosis. While we had information on the presence of ascites and/or hepatic encephalopathy indicating the presence of underlying liver dysfunction, SEER-Medicare does not contain laboratory data to allow for more precise quantification of liver dysfunction (e.g., to allow for calculation of MELD score and/or Child Pugh score), data on performance status, or sufficient tumor characteristics to determine Milan Criteria – factors that influence the likelihood of curative treatment and risk of mortality in patients with HCC. We characterized disparities in curative treatment receipt but did not examine receipt of palliative locoregional or systemic therapies, which can prolong survival albeit to a smaller degree than curative options.

We also acknowledge that our results should be interpreted cautiously due to heterogeneity within a race and ethnic group. For example, Asians and Pacific Islanders include ethnicities with stark differences and should not be mistaken for a monolith.

In conclusion, our study highlights that Black-White disparities persist in curative treatment utilization and overall survival among patients with HCC. This disparity appears to be moderated by neighborhood-level socioeconomic status, with the most significant differences noted among persons from high poverty areas. Future studies are needed to identify intervention targets to reduce disparities in HCC prognosis.

4. RACIAL, ETHNIC, AND SOCIOECONOMIC DISPARITIES IN TREATMENT DELAY AMONG PATIENTS WITH HEPATOCELLULAR CARCINOMA IN THE UNITED STATES

4.1. Introduction

Hepatocellular carcinoma (HCC) accounts for 75% to 85% of cases of primary liver cancer and is the third leading cause of cancer-related death worldwide.[72] With increased hepatitis B vaccination and hepatitis C treatment uptake worldwide, viral-related HCC is projected to decrease. However, in parallel with the high prevalence of metabolic syndrome, metabolic-associated fatty liver disease (MALFD)-related HCC is rapidly increasing in most countries, including the United States.[73]

Despite advances in treatment options, including expanded access to surgical therapies and improved systemic therapies, the 5-year survival for HCC remains poor at less than 20%.[52] This poor prognosis is partly related to failures occurring across the cancer care continuum, with several studies demonstrating underuse of HCC screening and treatment.[20,27,74,75] In addition, HCC disproportionately affects racial, ethnic, and low socioeconomic status (SES) populations, with both higher incidence and mortality, especially in Black and Hispanic patients.[5,7,21] However, few studies have characterized the prevalence of treatment delays and the potential association with survival in large, racially, and socioeconomically diverse populations.[28,62] These data are important as studies in breast and colorectal cancers have demonstrated that treatment delays are common and associated with worse survival.[76–78] Understanding the implications of

timely treatment for patients with HCC is particularly important in light of the COVID-19 pandemic, during which failures and delays in cancer treatment were common.[79]

The aims of our study were to (1) describe the prevalence and disparities in HCC treatment delay and (2) evaluate the association between treatment delay and overall survival in a large population-based sample of patients with HCC in the United States.

4.2. Methods

4.2.1. Data source and Study population

The National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database is a population-based dataset providing information on diagnosis, survival, demographics, and health services utilization of cancer patients from Medicare eligibility until death.[54] We included Medicare beneficiaries aged 65 years and older who had diagnostically confirmed HCC (International Classification of Diseases for Oncology, Third Edition, [ICD]- [O] histology code 8170 and site code C22.0 for the liver with positive histology, cytology, laboratory test, positive radiology tests) between the years 2001 and 2015.[80] Patients were excluded from the final sample if they: (1) were not continuously enrolled in Medicare Part A and B during the study period; (2) were enrolled in health maintenance organizations (HMOs)[54,81]; (3) were diagnosed with other cancers within one year prior to HCC diagnosis; (4) died within 30 days post HCC diagnosis; (5) had missing sociodemographic characteristics that could not be imputed or (6) did not receive any HCC treatment (**Supplemental Figure 1,** Appendix C).[81] This study protocol was

reviewed and deemed not human subjects research by the Institutional Review Board at Texas A&M University.

4.2.2. Sociodemographic and clinical predictors

We obtained patient sociodemographic information from the SEER Patient Entitlement and Diagnosis Summary File (PEDSF), including age, sex, race, ethnicity, census tract poverty level, geographic region, metropolitan status (using rural-urban continuum codes), and the year of HCC diagnosis. Based on prior literature, neighborhood SES was categorized based on census tract poverty level (0% to <10% poverty as low-poverty neighborhoods, 10% to <20% poverty as moderate-poverty neighborhoods, and ≥20% poverty as high-poverty neighborhoods).[26,58,82] Race and ethnicity were categorized as non-Hispanic White (White), non-Hispanic Black (Black), Hispanic, Asian/Pacific Islander (Asian), and "other/unknown."

Early-stage HCC was defined as a unifocal lesion ≤5 cm with no evidence of vascular invasion or distant metastases, as described previously.[83] We conducted a sensitivity analysis using the SEER stage, classified as localized, regional, or distant. In addition, we abstracted clinical information on liver disease etiology, ascites, and hepatic encephalopathy. Liver disease etiology was classified hierarchically as hepatitis C virus (HCV), hepatitis B virus (HBV), alcohol-related liver disease, other liver diseases (hemochromatosis, disorders of copper metabolism, porphyria), metabolic associated fatty liver disease (MAFLD), and no identifiable liver disease. MAFLD was defined by the presence of metabolic syndrome in the absence of other liver disease etiologies. NCI comorbidity index was used as a measure of non-cancer comorbidity.[59,60]

4.2.3. Outcomes and Statistical analysis

The primary outcome of interest was the presence of treatment delay, evaluated as a dichotomous variable, with delayed treatment defined as the time from diagnosis to first treatment exceeding three months, based on tumor doubling time and prior literature.[27,28,70,84] HCC-specific treatments were abstracted from Medicare claims data using the International Classification of Diseases, ninth and tenth Revision, Clinical Modification (ICD-9, ICD-10-Procedure Coding System), HCPCS, and Current Procedure Terminology (CPT) codes within 12 months post HCC diagnosis. HCC treatments were then categorized into the most definitive treatment, defined hierarchically as liver transplantation, surgical resection, local ablation, transarterial embolization, radiation, and systemic therapy, respectively. Chi-square tests were used to compare characteristics of the study population between those who received timely treatment (i.e., within 3 months) versus delayed treatment (i.e., exceeding 3 months). We then performed multivariable logistic regression, with an interaction between race, ethnicity, and SES with time fixed effects, to examine the association between race and ethnicity with treatment delay across socioeconomic strata. We adjusted standard errors for clustering at the census tract level.

We conducted landmark analysis to examine our secondary outcome of overall survival, accounting for immortal time bias.[85,86] Overall survival was defined as the time from the landmark to death from any cause. A landmark of 5 months was selected for the primary analysis based on prior literature.[27] Patients whose HCC was treated within or at 3 months were classified as timely treatment, those who received therapy between 4-5

months were classified as delayed treatment, and those who received therapy later than 5 months were excluded from this analysis. Patients who died prior to the 5-month landmark were also excluded from the analysis. Patients who remained alive on December 31, 2017, were censored at that date. We performed univariable and multivariable Cox proportional hazards analyses to examine the association between treatment delay and overall survival.

All *p*-values were two-sided with a statistical significance of 5%. All statistical analyses were performed using Stata version 16.1 (Stata Corp, College Station, TX).

4.3. Results

4.3.1. Patient characteristics

Of 13,874 patients with HCC, 8,450 (60.9%) were treated within 12 months of diagnosis (**Supplemental Figure 1,** Appendix C). The median age was 73 years, and more than two-thirds (67.2%) were male. The racial and ethnic composition of the cohort was 68.1% White, 7.4% Black, 13.4% Asian, and 4.0% Hispanic patients. Most patients resided in low-poverty neighborhoods (48.2%) and in metropolitan areas with more than 1 million people (62.7%). The most common underlying liver disease etiology was MAFLD (36.4%), followed by HCV (31.0%). More than half of patients (60.4%) were identified as having localized SEER stage; however, only 23.1% had a unifocal lesion ≤5 cm without vascular invasion or distant metastases.

4.3.2. Prevalence and Correlates of Treatment Delay

The median time from HCC diagnosis to first treatment was 1 (IQR 1 to 3) month, with treatment delays observed in 1205 (14.3%) patients. The proportion of patients with delayed treatment remained stable over the study period (**Figure 11**).

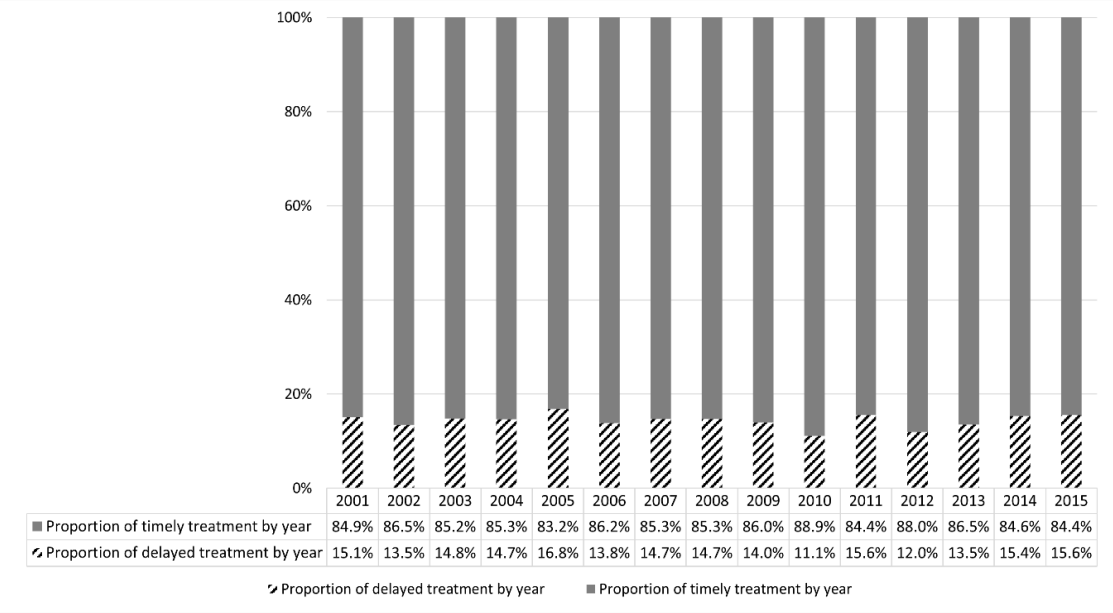

Figure 11. Proportion of patients with delayed and timely treatment by years.

Characteristics of patients receiving timely versus delayed treatment are shown in **Table** 8.

Table 8. Characteristics of patients receiving timely versus delayed treatment

	Patients receiving timely treatment n=7245		Patients receiving delayed treatment n=1205		*P* value
	n	%	n	%	
Total	7245	100.0%	1205	100.0%	
Age at diagnosis					<0.001
65 - 69 years	1940	26.8%	390	32.4%	
70 - 74 years	2065	28.5%	369	30.6%	
75 - 79 years	1727	23.8%	232	19.3%	
80 years and older	1513	20.9%	214	17.8%	
Gender					0.86
Female	2382	32.9%	393	32.6%	
Male	4863	67.1%	812	67.4%	
Race and ethnicity					<0.001
White	4986	68.8%	771	64.0%	
Black	498	6.9%	124	10.3%	
Asian	967	13.3%	165	13.7%	
Hispanic	276	3.8%	61	5.1%	
Other/Unknown	518	7.1%	84	7.0%	
Neighborhood-level SES					<0.001
Low poverty neighborhoods	3558	49.1%	518	43.0%	
Moderate poverty neighborhoods	2093	28.9%	381	31.6%	
High poverty neighborhoods	1594	22.0%	306	25.4%	
Geographic region					<0.001
Northeast	1338	18.5%	228	18.9%	
West	3792	52.3%	696	57.8%	
Midwest	691	9.5%	101	8.4%	
South	1424	19.7%	180	14.9%	
Metropolitan status					0.02
Metro > 1 million	4549	62.8%	750	62.2%	
Metro 250,000 - 1 million	1415	19.5%	255	21.2%	
Metro <250,000	522	7.2%	103	8.5%	
Non-Metro	759	10.5%	97	8.0%	
Tumor Staging					<0.001
Unifocal <=5 cm without vascular invasion and metastasis	1642	22.7%	310	25.7%	
Beyond unifocal without vascular invasion and metastasis	3605	49.8%	641	53.2%	
Vascular invasion or metastasis	313	4.3%	50	4.1%	
Non-determinable	1685	23.3%	204	16.9%	

Table 8. Continued.

	Patients receiving timely treatment n=7245		Patients receiving delayed treatment n=1205		*P* value
	n	%	n	%	
SEER stage					0.01
Localized	4531	62.5%	751	62.3%	
Regional	1753	24.2%	298	24.7%	
Distant	766	10.6%	90	7.5%	
Unknown	375	5.2%	66	5.5%	
NCI comorbidity index					0.001
0	1566	21.6%	237	19.7%	
1	1601	22.1%	218	18.1%	
2	1422	19.6%	245	20.3%	
3	1315	18.2%	259	21.5%	
4	405	5.6%	85	7.1%	
>=5	936	12.9%	161	13.4%	
Liver disease etiology					<0.001
HCV	2175	30.0%	448	37.2%	
HBV	402	5.5%	59	4.9%	
Alcohol related liver disease	737	10.2%	137	11.4%	
Other liver diseases	148	2.0%	25	2.1%	
MAFLD	2705	37.3%	372	30.9%	
No identifiable liver disease	1078	14.9%	164	13.6%	
Liver dysfunction					
Presence of hepatic encephalopathy	476	6.6%	80	6.6%	0.93
Presence of ascites	900	12.4%	149	12.4%	0.96

Patients receiving delayed treatment were more likely to be Black, reside in poorer neighborhoods, have a higher comorbidity burden, and have underlying hepatitis C infection.

The proportion of patients experiencing treatment delays differed by type of HCC therapy, with the highest delays observed in patients who underwent liver transplantation and lowest in those treated with surgical resection (**Figure 12**).

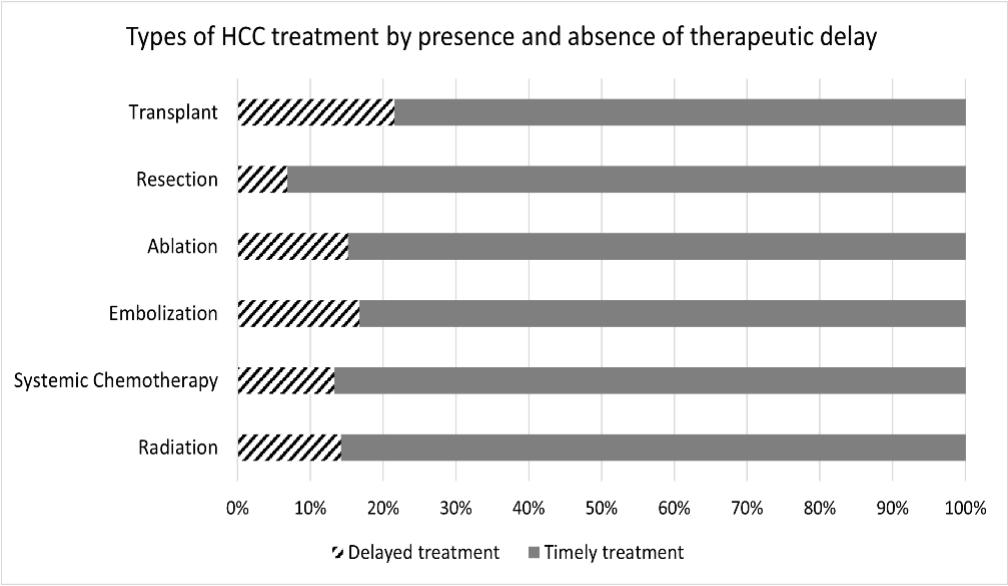

Figure 12. Types of HCC treatments by presence and absence of therapeutic delay.

Among the 480 patients who underwent liver transplantation, 153 had transplantation as the initial therapy, and 327 had received prior bridging therapy. Of those who underwent bridging therapy, 14.2% had treatment delays, with bridging therapy occurring more than three months after HCC diagnosis. We also noted sociodemographic disparities in time-to-treatment. Treatment delays were observed in 19.9% of Black and 18.1% of Hispanic patients, compared to 13.4% and 14.6% of White and Asian patients, respectively. Similarly, treatment delays were observed in 12.7%, 15.4%, and 16.1% of those living in low, moderate, and high poverty neighborhoods, respectively.

In multivariable analysis (**Table 9**), we continued to observe sociodemographic disparities in treatment delays. Specifically, Black patients (OR 1.91 95%CI 1.20 – 3.05)

and patients living in moderate-high poverty neighborhoods (moderate poverty neighborhood: OR 1.30 95%CI 1.08 – 1.57; high poverty neighborhoods: OR 1.53 95%CI 1.24 – 1.89) were more likely to experience treatment delays compared to White patients and those living in low poverty neighborhoods, respectively. The interaction between the Black race and neighborhood poverty was not statistically significant.

Table 9. Correlates of delayed treatment (with and without type of first HCC treatment).

	Delayed treatment (without first HCC treatment) n=8450 OR (95% CI)[5]	Delayed treatment (with first HCC treatment) n=8450 OR (95% CI)[6]
Age at diagnosis		
65 - 69 years	Ref	Ref
70 - 74 years	0.94 (0.80,1.10)	0.95 (0.81,1.12)
75 - 79 years	0.71 (0.59,0.85)	0.72 (0.60,0.86)
80 years and older	0.78 (0.65,0.95)	0.77 (0.63,0.93)
Male sex	1.03 (0.90,1.17)	1.02 (0.89,1.16)
Race and ethnicity		
White	Ref	Ref
Black	1.91 (1.20,3.05)	1.96 (1.21,3.15)
Asian	1.27 (0.96,1.68)	1.30 (0.98,1.72)
Hispanic	1.02 (0.53,1.97)	1.02 (0.53,1.96)
Other/Unknown	1.01 (0.70,1.45)	1.02 (0.71,1.45)
Neighborhood-level SES		
Affluent neighborhoods	Ref	Ref
Moderate poverty neighborhoods	1.30 (1.08,1.57)	1.29 (1.07,1.55)
Poor neighborhoods	1.53 (1.24,1.89)	1.55 (1.25,1.92)

[5] Model included year fixed effects (not reported)
[6] Model included year fixed effects (not reported)

Table 9. Continued.

	Delayed treatment (without first HCC treatment) n=8450 OR (95% CI)	Delayed treatment (with first HCC treatment) n=8450 OR (95% CI)
Interaction of race, ethnicity, and poverty		
Black#Moderate poverty neighborhoods	0.72 (0.40,1.32)	0.71 (0.39,1.32)
Black#High poverty neighborhoods	0.61 (0.34,1.08)	0.59 (0.33,1.06)
Asian#Moderate poverty neighborhoods	0.82 (0.54,1.25)	0.82 (0.54,1.26)
Asian#High poverty neighborhoods	0.44 (0.26,0.74)	0.44 (0.26,0.73)
Hispanic#Moderate poverty neighborhoods	1.63 (0.72,3.69)	1.58 (0.70,3.58)
Hispanic#High poverty neighborhoods	0.83 (0.37,1.85)	0.82 (0.37,1.83)
Geographic region		
West	Ref	Ref
Northeast	1.05 (0.88,1.26)	1.07 (0.89,1.28)
Midwest	0.83 (0.66,1.05)	0.82 (0.65,1.04)
South	0.65 (0.54,0.79)	0.65 (0.54,0.79)
Metropolitan status		
Metro > 1 million	Ref	Ref
Metro 250,000 - 1 million	1.10 (0.94,1.28)	1.10 (0.94,1.29)
Metro <250,000	1.29 (1.01,1.65)	1.29 (1.00,1.66)
Non-Metro	0.87 (0.69,1.09)	0.88 (0.69,1.11)
Tumor Staging		
Unifocal <=5 cm without vascular invasion and metastasis	Ref	Ref
Beyond unifocal without vascular invasion and metastasis	1.00 (0.86,1.16)	0.95 (0.81,1.11)
Vascular invasion or metastasis	0.89 (0.60,1.32)	0.83 (0.55,1.26)
NCI comorbidity index		
0	Ref	Ref
1	0.93 (0.76,1.15)	0.92 (0.75,1.14)
2	1.05 (0.86,1.29)	1.01 (0.82,1.24)
3	1.18 (0.96,1.45)	1.12 (0.91,1.38)
4	1.35 (1.02,1.78)	1.31 (0.99,1.73)
>=5	1.06 (0.84,1.34)	1.01 (0.80,1.28)

Table 9. Continued.

Liver disease etiology		
HCV	Ref	Ref
HBV	0.74 (0.55,1.01)	0.79 (0.58,1.07)
Alcohol related liver disease	1.02 (0.81,1.27)	1.00 (0.80,1.24)
Other liver diseases	0.99 (0.64,1.54)	1.02 (0.66,1.57)
MAFLD	0.81 (0.68,0.95)	0.85 (0.72,1.00)
No identifiable liver disease	0.87 (0.69,1.09)	0.92 (0.73,1.15)
Liver dysfunction		
Presence of hepatic encephalopathy	0.88 (0.68,1.15)	0.82 (0.63,1.07)
Presence of ascites	0.89 (0.72,1.10)	0.86 (0.70,1.07)
First HCC treatment type		
Liver transplantation		1.24 (0.82,1.87)
Surgical resection		0.38 (0.29,0.49)
Local ablation		0.81 (0.68,0.98)
Embolization		Ref
Systemic chemotherapy		0.81 (0.69,0.96)
Radiation		0.90 (0.68,1.20)

4.3.3. Overall Survival

In the 5-month landmark analysis (n=6335), 5668 patients (89.5%) received timely treatment while 677 patients (10.5%) received delayed treatment. The median overall survival of the cohort was 27 (IQR 13 to 64) months – 28 months for patients with timely treatment compared to 24 months for those with treatment delay. Treatment delay was associated with worse survival in univariable (HR 1.16 95% CI 1.07 – 1.27) (**Figure 13)** and multivariable (HR 1.17, 95%CI 1.08 – 1.28) analyses.

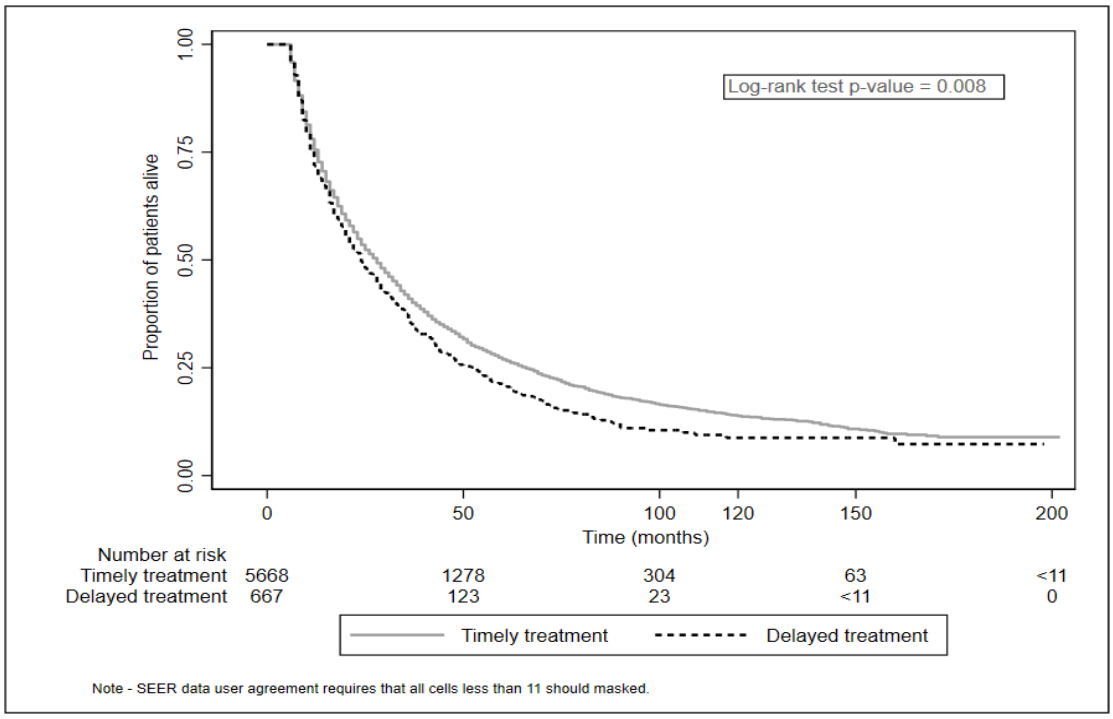

Figure 13. Overall unadjusted survival – delayed vs. timely treatment.

In multivariable analysis (**Table 10**), compared to White patients, Hispanic patients had worse survival (HR 1.35 95%CI 1.03 – 1.77), whereas Asian patients had better survival (HR 0.81 95% CI 0.72 – 0.92).

Table 10. Correlates of overall survival – 5 – month landmark (without and with type of first treatment).

	Overall survival (Without first HCC treatment) n=6335 HR (95% CI)	Overall survival (with first HCC treatment) n=6335 HR (95% CI)
Delayed treatment	1.17 (1.08,1.28)	1.09 (1.00,1.20)

Table 10. Continued.

	Overall survival (Without first HCC treatment) n=6335 HR (95% CI)	Overall survival (with first HCC treatment) n=6335 HR (95% CI)
Age at diagnosis		
65 - 69 years	Ref	Ref
70 - 74 years	1.16 (1.07,1.26)	1.16 (1.07,1.26)
75 - 79 years	1.31 (1.21,1.42)	1.26 (1.16,1.37)
80 years and older	1.48 (1.36,1.61)	1.39 (1.28,1.52)
Male	1.12 (1.05,1.20)	1.10 (1.03,1.18)
Race and ethnicity		
White	Ref	Ref
Black	0.84 (0.63,1.12)	0.79 (0.58,1.08)
Asian	0.81 (0.72,0.92)	0.78 (0.68,0.88)
Hispanic	1.35 (1.03,1.77)	1.27 (0.98,1.65)
Other/Unknown	0.72 (0.61,0.86)	0.75 (0.63,0.88)
Neighborhood-level SES		
Low poverty neighborhoods	Ref	Ref
Moderate poverty neighborhoods	1.02 (0.94,1.11)	1.00 (0.93,1.09)
High poverty neighborhoods	1.09 (0.98,1.21)	1.04 (0.94,1.16)
Interaction of race, ethnicity, and poverty		
Black#Moderate poverty neighborhoods	1.19 (0.85,1.69)	1.21 (0.84,1.74)
Black#High poverty neighborhoods	1.36 (0.98,1.90)	1.34 (0.94,1.91)
Asian#Moderate poverty neighborhoods	1.05 (0.87,1.26)	1.11 (0.92,1.34)
Asian#High poverty neighborhoods	0.87 (0.70,1.10)	0.91 (0.71,1.16)
Hispanic#Moderate poverty neighborhoods	1.04 (0.73,1.48)	1.05 (0.75,1.48)
Hispanic#High poverty neighborhoods	0.72 (0.51,1.02)	0.72 (0.51,1.01)
Geographic region		
West	Ref	Ref
Northeast	0.95 (0.88,1.03)	0.98 (0.91,1.07)
Midwest	1.12 (1.01,1.25)	1.14 (1.02,1.28)
South	1.07 (0.98,1.18)	1.16 (1.06,1.27)
Metropolitan status		
Metro > 1 million	Ref	Ref
Metro 250,000 - 1 million	1.03 (0.95,1.11)	1.02 (0.95,1.10)
Metro <250,000	1.00 (0.89,1.13)	0.96 (0.85,1.09)
Non-Metro	0.89 (0.80,0.99)	0.90 (0.80,1.00)

Table 10. Continued.

Geographic region		
West	Ref	Ref
Northeast	0.95 (0.88,1.03)	0.98 (0.91,1.07)
Midwest	1.12 (1.01,1.25)	1.14 (1.02,1.28)
South	1.07 (0.98,1.18)	1.16 (1.06,1.27)
Metropolitan status		
Metro > 1 million	Ref	Ref
Metro 250,000 - 1 million	1.03 (0.95,1.11)	1.02 (0.95,1.10)
Metro <250,000	1.00 (0.89,1.13)	0.96 (0.85,1.09)
Non-Metro	0.89 (0.80,0.99)	0.90 (0.80,1.00)
Tumor Staging		
Unifocal <=5 cm without vascular invasion and metastasis	Ref	Ref
Beyond unifocal without vascular invasion and metastasis	1.55 (1.44,1.66)	1.44 (1.34,1.55)
Vascular invasion or metastasis	2.11 (1.82,2.45)	2.13 (1.81,2.51)
Non-determinable	1.88 (1.72,2.05)	1.77 (1.62,1.94)
NCI comorbidity index		
0	Ref	Ref
1	1.04 (0.94,1.13)	1.04 (0.95,1.15)
2	1.04 (0.94,1.14)	1.04 (0.94,1.14)
3	1.07 (0.97,1.18)	1.09 (0.98,1.20)
4	1.22 (1.07,1.39)	1.16 (1.00,1.33)
>=5	1.27 (1.13,1.42)	1.22 (1.09,1.37)
Liver disease etiology		
HCV	Ref	Ref
HBV	0.69 (0.60,0.79)	0.72 (0.62,0.83)
Alcohol related liver disease	1.07 (0.96,1.19)	1.06 (0.96,1.18)
Other liver diseases	0.93 (0.76,1.14)	0.99 (0.81,1.21)
MAFLD	0.98 (0.91,1.06)	1.02 (0.95,1.11)
No identifiable liver disease	1.05 (0.95,1.17)	1.12 (1.00,1.24)
Liver dysfunction		
Presence of hepatic encephalopathy	1.06 (0.92,1.21)	1.08 (0.95,1.24)
Presence of ascites	1.15 (1.04,1.27)	1.07 (0.96,1.19)
First HCC treatment type		
Liver transplantation		0.33 (0.25,0.42)
Surgical resection		0.50 (0.46,0.54)
Local ablation		0.83 (0.77,0.91)
Embolization		Ref
Systemic chemotherapy		1.52 (1.39,1.65)
Radiation		1.48 (1.25,1.74)

There was no statistically significant difference in survival between Black patients and White patients. Median overall survival was 38 months for Asian patients compared to 25, 23, and 22 months for White, Black, and Hispanic patients, respectively. Other factors associated with worse survival included male sex, older age ≥70 years, higher comorbidity, presence of ascites, more advanced tumor burden, living in the Midwest, and living in non-metropolitan areas. When the type of HCC treatment was added to the multivariable analysis, treatment delay continued to be associated with worse survival**.**

In subgroup analyses by tumor stage **(Supplemental Table 1 and 2,** Appendix C), treatment delay was associated with worse survival for patients with early-stage HCC (HR 1.22 95%CI 1.02 – 1.46), although this was no longer statistically significant when the type of HCC treatment was added to the model (HR 1.12 95%CI 0.93 – 1.35). In non-early-stage patients, treatment delay was associated with higher mortality in both models (**Supplemental Table 2,** Appendix C). We also conducted subgroup analyses by curative (i.e., surgical resection, local ablation, liver transplantation) vs. non-curative treatment (i.e., embolization, radiation, and systemic therapy). Delayed treatment was associated with worse survival among patients who received curative treatment, although this association was mitigated when the type of HCC treatment was added to the model (**Supplemental Table 3**). For non-curative treatments, delayed treatment was not associated with overall survival in either model (**Supplemental Table 4,** Appendix C). Sensitivity analyses using SEER staging (i.e., local, regional, distant) yielded similar results (data not shown).

4.4. Discussion

In this population-based sample, we found that nearly one in seven patients with HCC experience treatment delays exceeding 3 months. Several sociodemographic factors were associated with treatment delay; Black patients and those living in moderate and high poverty neighborhoods were more likely to experience treatment delays than White patients and those living in low poverty neighborhoods, respectively. These findings are notable given the association between treatment delay and worse overall survival, highlighting a need for interventions to improve time-to-treatment for patients newly diagnosed with HCC.

Prior studies have described racial and socioeconomic disparities in HCC treatment utilization and overall survival.[20,32,33] In a previous study using the SEER-Medicare database, we found Black patients were less likely to receive curative treatment and had higher mortality, particularly those in high poverty neighborhoods compared to White patients living in similar neighborhoods.[83] The current study extends this work by demonstrating continued racial and ethnic disparities in treatment delays and survival even in this selected population of Medicare beneficiaries. Further, our findings are consistent with a recent study conducted in the VA system; taken together this data indicates that insurance status alone cannot account for observed disparities in HCC outcomes.[87] This is also consistent with prior studies that have demonstrated significant racial and ethnic disparities among Medicare enrollees in most adverse health indicators, receipt of timely cancer screening, and in the patient experience of care coordination.[88–90] This persistent disparity is likely in part related to socioeconomic

factors; for example, racial and ethnic minority patients are less likely than Whites to have supplemental coverage to cover gaps in Medicare coverage. [91]

Racial, ethnic, and socioeconomic disparities in care delivery are well documented in other cancers and can be due to a combination of patient, provider, and system-level factors. Although we found several patient-related factors associated with treatment delays, we could not evaluate other important factors, including patient knowledge, attitudes (e.g., level of concern and health locus of control), and barriers to care such as medical mistrust, transportation, and financial barriers.[92,93] There are also several provider-level factors that can impact cancer care delivery, including cultural barriers, implicit biases against minority populations, and resource constraints faced by providers caring for a greater proportion of disadvantaged patients.[46,94] Finally, system-level factors such as resource constraint, scheduling issues, and lack of care coordination may lead to longer wait times and exacerbate disparities in treatment delays even among those with Medicare coverage [95]. On a broad scale, some of the inequities observed in this population can be attributed to structural socioeconomic and environmental factors rooted in discrimination and systemic racism.[96] For example, in a survey study of over 230,000 Medicare beneficiaries, Black and Hispanic patients reported more difficulty receiving timely follow-up on test results and less help managing their care than White patients.[90] Prior studies have also demonstrated wide variability in racial and ethnic disparities in the Medicare population across regions and for different procedures.[97] Future studies are needed to assess how these factors impact time to HCC treatment in different practice settings. While expanding Medicare coverage to all would positively

impact improving accessibility to cancer care, other issues impacting cancer care disparities must also be addressed, including access to telemedicine, neighborhood conditions, food insecurity, and financial opportunities.[98]

Prior studies in HCC have had discordant findings regarding the association between treatment delays and survival.[27–29] This discordance may be partly related to specific reasons for treatment delay and the type of HCC treatment delivered. For example, providers may be more likely to closely monitor patients and delay treatment in patients with small or slow-growing indolent tumors. Similarly, providers may defer treatment in patients with significant liver dysfunction who are actively listed for liver transplantation. In our 5-month landmark analysis accounting for immortal time bias, we found that HCC treatment delay exceeding 3 months was associated with worse survival. This finding is consistent with prior studies examining the impact of treatment delay on survival in other cancers, including breast and colorectal cancer.[76–78,99,100]

Strengths of our study include using a large population-based dataset with linkage to Medicare claims to provide treatment information, liver dysfunction parameters, and liver disease etiology, as well as our use of a landmark analysis to mitigate potential immortal time bias.[101] However, we acknowledge the limitations of the study. We excluded patients younger than 65 years and did not have access to all the states through the SEER registry, limiting the generalizability of the findings.[54] Additionally, SEER-Medicare does not have sufficiently granular data to assess Child-Pugh or MELD scores, performance status, or tumor characteristics to determine Milan Criteria or Barcelona Clinic Liver Cancer staging. Finally, our findings describing racial

and ethnic disparities should be interpreted cautiously, as race and ethnicity are self-reported in SEER and do not account for multiracial and/or multiethnic patients.[101]

In conclusion, our study highlights that treatment delays are experienced by 10-20% of patients, with observed racial, ethnic, and socioeconomic disparities. Given an association between treatment delays and overall survival, interventions to reduce these disparities remain critical.

5. CONCLUSION

This dissertation addresses gaps in the current HCC treatment disparities among racial-ethnic minority groups in the United States through three aims: (1) characterizing and quantifying racial-ethnic disparities in treatment receipt among patients with HCC in the United States through a meta-analysis; (2) characterizing the interaction of racial, ethnic, and neighborhood socioeconomic disparities in curative treatment use and overall survival in the United States among a large population-based sample of patients with HCC (3) describing the prevalence and disparities in HCC treatment delay and evaluating the association between treatment delay and overall survival in a large population-based sample of patients with HCC in the United States.

The first study of this dissertation utilizes a validated health equity filter to capture all studies focusing on disparities within receipt of HCC-specific treatment. This study demonstrates that Black patients have lower pooled odds of receiving curative and any HCC treatment when compared to White patients. Additionally, Hispanic patients have lower pooled odds of receiving curative treatment when compared to White patients. This study indicates that despite the advances in HCC treatment, racial-ethnic disparities still exist and draws the attention of clinicians and researchers to design interventions that seek to reduce these disparities.

The second study of this dissertation adds to the current literature by demonstrating that the interplay between race, ethnicity, and area-based SES impacts receipt of curative treatment. Black patients in high-poverty neighborhoods have lower

odds of receiving treatment and subsequently worse survival. This study demonstrates that having insurance coverage like Medicare may not be enough to reduce racial-ethnic and socioeconomic disparities in receipt of curative treatment. More studies are needed to understand mediating pathways that exacerbate racial-ethnic disparities within the HCC care continuum.

The third study of this dissertation adds to the current literature by describing the prevalence of HCC-specific treatment delay, characterizing disparities within treatment delay, examining the association of treatment delay and overall survival utilizing a large population-based cohort in the United States. Black patients and those living in high poverty neighborhoods experience higher treatment delays when compared to White patients and those living in low poverty neighborhoods, respectively. Moreover, treatment delay is associated with worse overall survival among HCC patients.

SDOH have a critical role in determining patient success from diagnosis of cancer to survivorship. SDOH like poverty, immigration status, lack of education, and social isolation have shown to have a negative impact on overall survival in patients with breast and colorectal cancer. [17,18] This dissertation attempts to bring attention to SDOH like neighborhood SES and its interaction with race-ethnicity and the overall impact of this intersectionality on HCC treatment. We believe that researchers and clinicians working in the field of HCC will design future studies to better understand SDOH and their impact on the HCC care continuum.

5.1. Future work

Despite the advances in HCC care, racial-ethnic disparities continue to exist, and these populations continue to have worse outcomes. The first study can be expanded to include literature published from January 2021 to February 2022 to capture additional studies focusing on racial-ethnic disparities within receipt of HCC-specific treatment. Subgroup analysis of early-stage HCC patients and definition of curative treatment (if data available) for disparities and treatment rate models could be added.

Social determinants of health (SDOH) like poverty, racism, health literacy, environmental stress, and social support are likely to impact patient access to care and subsequent outcomes.[13,14,16,19] However, the intersectionality of such factors with race-ethnicity is not well studied within the HCC care continuum. Hence, future studies are needed to examine this intersectionality closely to develop interventions that seek to reduce disparities and achieve equitable outcomes among marginalized HCC patients.

Furthermore, issues within the patient-provider relationship have been known to affect treatment course and subsequent outcomes in cancer patients.[46] A patient's cultural background can invoke implicit bias and affect the course of their care.[47–50] Future studies should seek to understand how cultural barriers and provider bias affect receipt of HCC treatment among traditionally marginalized communities in the US.

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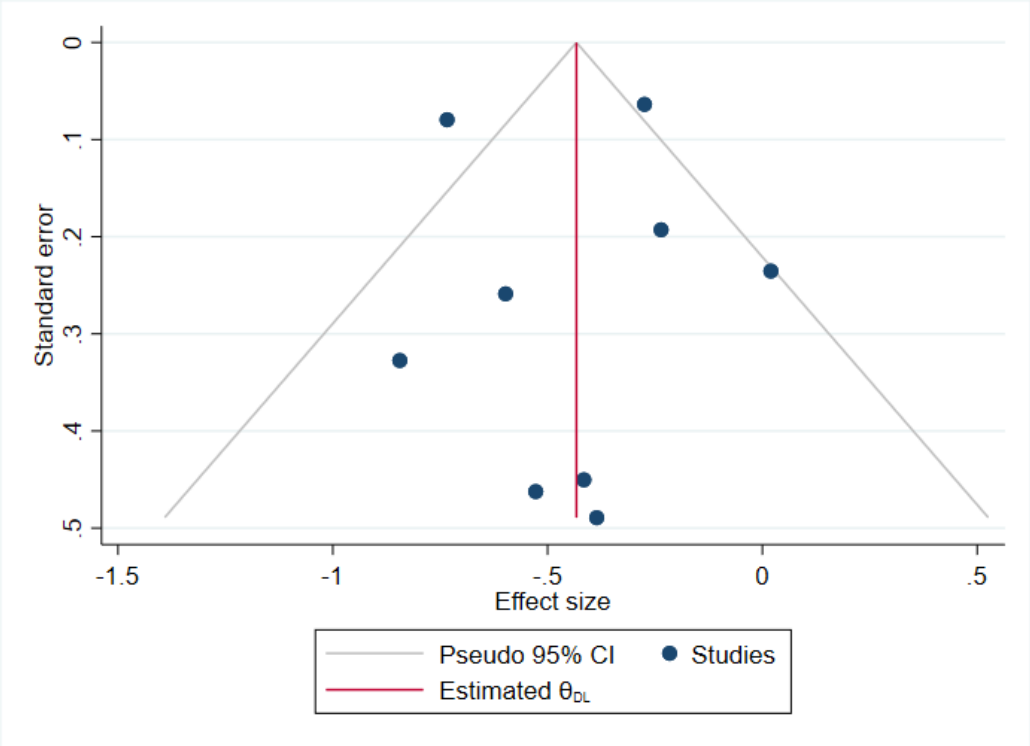
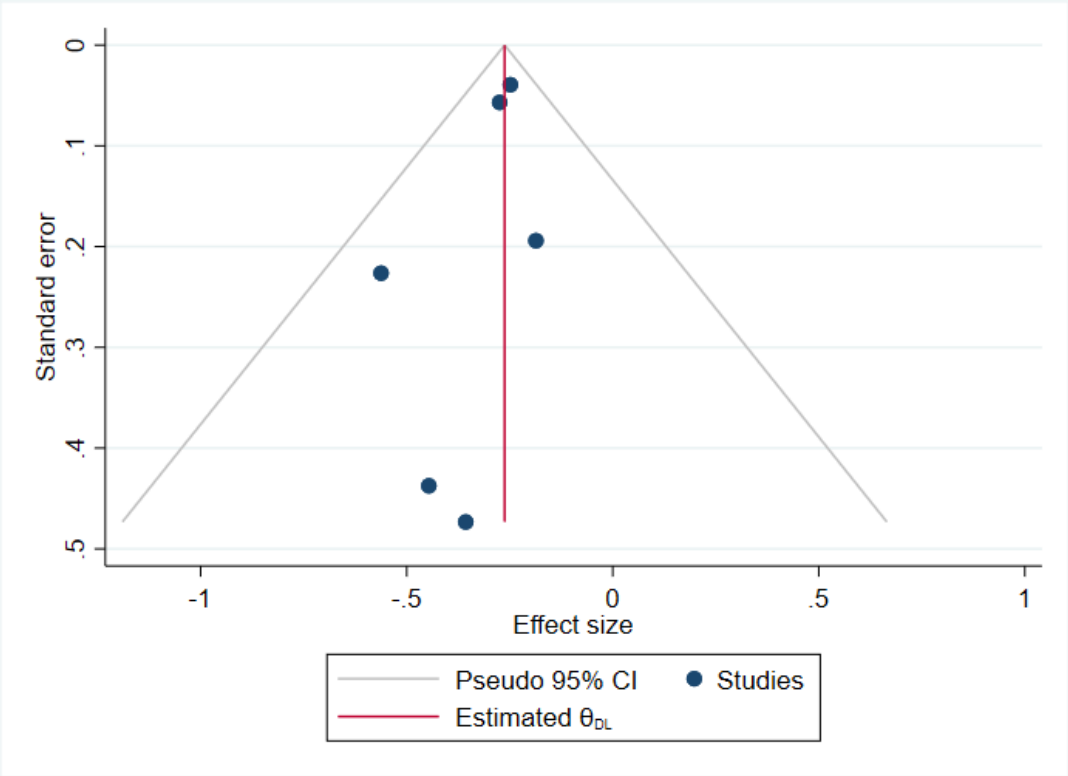
7. APPENDIX A

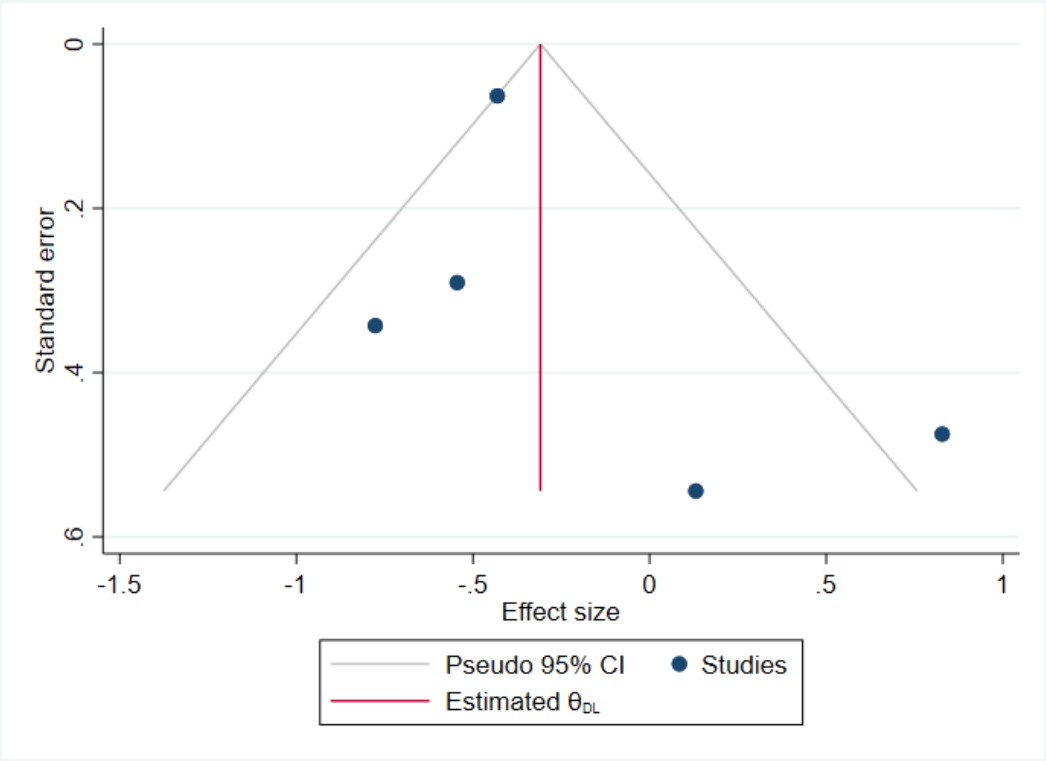
7.1. Supplemental Figures



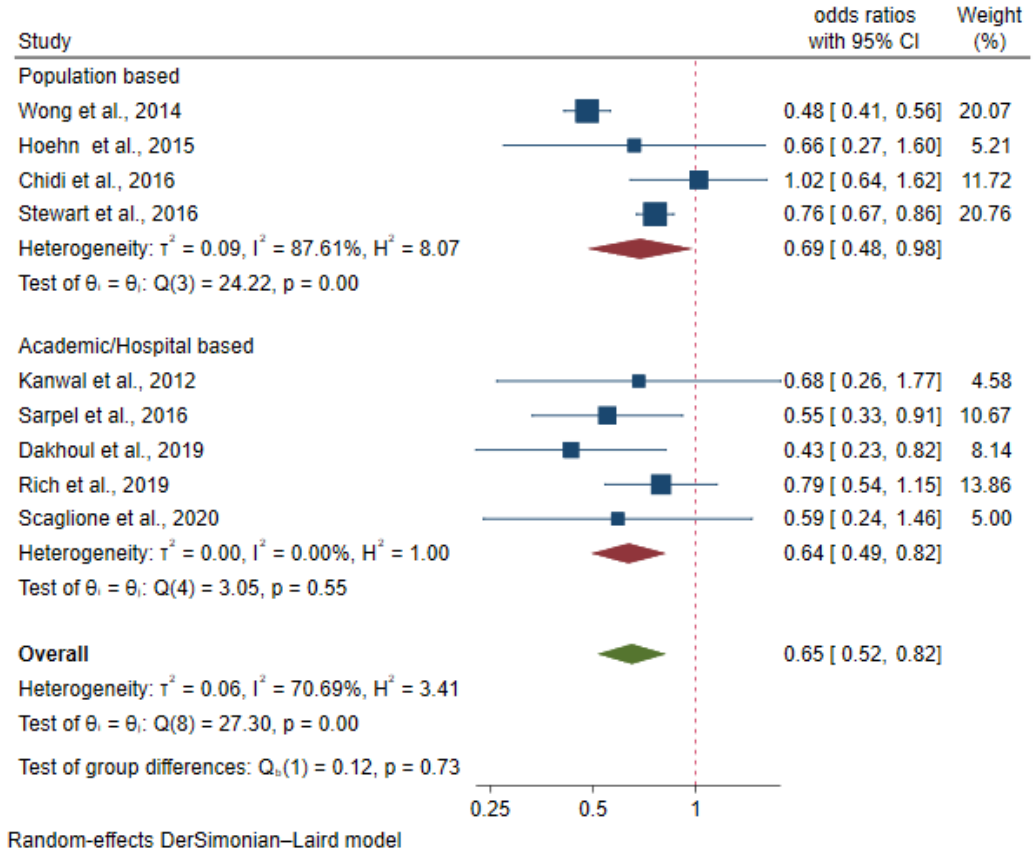
Supplemental Figure 1. Funnel plot for Black-White disparities in curative treatment receipt.



Supplemental Figure 2. Funnel plot for Hispanic-White disparities in curative treatment receipt.



Supplemental Figure 3. Funnel plot for Asian-White disparities in curative treatment receipt.



Supplemental Figure 4. Subgroup analysis for Black-White disparities within receipt of curative treatment.

7.2. Supplemental tables

Supplemental Table 1. Definitions and rates of curative treatment receipt.

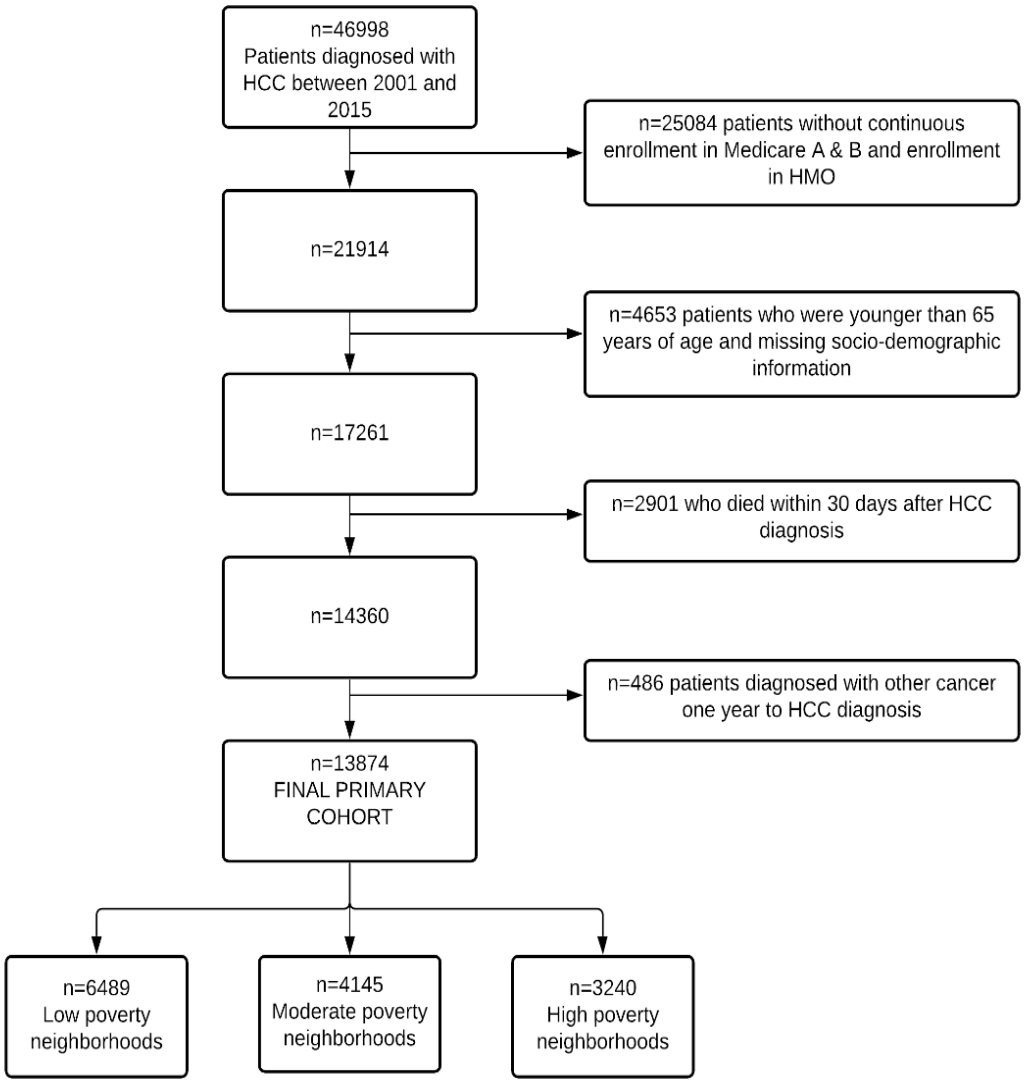
Study	HCC patients (n)	Curative treatment receipt (n)	Curative treatment rate (%)	Definition of curative treatment
Kanwal et al., 2012	267	122	45.69%	OLT, Resection, Ablation
Wong et al., 2012	575	56	9.73%	OLT
Davila et al., 2013	1296	152	11.73%	OLT, Surgical Resection, Local Ablation
Singal et al., 2013	267	NR	NR	
Wong et al., 2014	60772	13540	22.28%	OLT, Resection, Local tumor destruction
Hoehn et al., 2015	143692	31804	22.13%	Surgery
Chidi et al., 2016	3576	1276	35.68%	Surgery
Sarpel et al., 2016	754	289	38.33%	OLT
Stewart et al., 2016	33270	6636	19.95%	Surgery
Kokabi et al., 2017	9368	NR	NR	
Dakhoul et al., 2019	1196	NR	NR	
Rich et al., 2019	1117	322	28.83%	OLT, Resection, Ablation
Scaglione et al., 2020	379	102	26.91%	OLT, Resection, Ablation

Supplemental Table 2. Definitions and rates of any treatment.

Study	HCC patients (n)	Any HCC treatment (n)	Any HCC treatment (%)	Definition of any treatment
Kanwal et al., 2012	267	163	61.05%	OLT, Surgical resection, Tumor ablation, TACE, Other
Wong et al., 2012	575	NR	NR	
Davila et al., 2013	1296	445	34.34%	Liver transplantation, Surgical Resection, Local Ablation, TACE or Systemic Chemotherapy
Wong et al., 2014	60772	NR	NR	
Hoehn et al., 2015	143692	NR	NR	
Chidi et al., 2016	3576	NR	NR	
Sarpel et al., 2016	3078	NR	NR	
Stewart et al., 2016	33270	NR	NR	
Dakhoul et al., 2019	1196	NR	NR	
Rich et al., 2019	1117	742	66.43%	OLT, Resection, Local ablation, TACE/TARE/SBRT, Systemic therapy
Scaglione et al., 2020	379	265	69.92%	OLT, Surgical resection, Local ablative therapy, TACE/TARE, Systemic therapy

8. APPENDIX B

8.1. Supplemental Figures



Supplemental Figure 1. Sample Flow.

8.2. Supplemental Tables

Supplemental Table 1. Factors associated with receipt of curative treatment.

	Curative treatment				*P*
	Not received (n=11257) Number, %		**Received** (n=2617) Number, %		
Age at diagnosis					
65 years – 69 years	2608	23.2%	830	31.7%	
70 years – 74 years	2867	25.5%	798	30.5%	
75 years – 79 years	2678	23.8%	566	21.6%	<0.001
80 years and over	3104	27.6%	423	16.2%	
Gender					<0.001
Female	3509	31.2%	933	35.7%	
Male	7748	68.8%	1684	64.3%	
Race and ethnicity					<0.001
White	7814	69.4%	1780	68.0%	
Black	972	8.6%	189	7.2%	
Asian	1328	11.8%	347	13.3%	
Hispanic	487	4.3%	86	3.3%	
Other/Unknown	656	5.8%	215	8.2%	
Neighborhood-level SES					<0.001
Low poverty neighborhoods	5159	45.8%	1330	50.8%	
Moderate poverty neighborhoods	3428	30.5%	717	27.4%	
High poverty neighborhoods	2670	23.7%	570	21.8%	
Census tract education level (mean, standard deviation)	18.02	13.71	16.23	13.00	
Geographic region					0.042
Northeast	1955	17.4%	514	19.6%	
West	6005	53.3%	1372	52.4%	
Midwest	1099	9.8%	235	9.0%	
South	2198	19.5%	496	19.0%	
Abdominal ultrasound					<0.001
No	7127	63.3%	1336	51.1%	
Yes	4130	36.7%	1281	48.9%	
Unifocal lesion					<0.001
No	5490	48.8%	1113	42.5%	
Yes	1546	13.7%	911	34.8%	
Non-determinable	4221	37.5%	593	22.7%	
SEER Stage					<0.001
Localized	5267	46.8%	2023	77.3%	
Regional	3151	28.0%	441	16.9%	
Distant	1704	15.1%	60	2.3%	
Unknown	1135	10.1%	93	3.6%	

NCI comorbidity index					<0.001
0	2633	23.4%	553	21.1%	
1	2455	21.8%	519	19.8%	
2	1803	16.0%	569	21.7%	
3	1784	15.8%	528	20.2%	
4	678	6.0%	153	5.8%	
>=5	1904	16.9%	295	11.3%	
Liver disease etiology					<0.001
HCV	2688	23.9%	901	34.4%	
HBV	401	3.6%	186	7.1%	
Alcohol related liver disease	1155	10.3%	224	8.6%	
Other	185	1.6%	59	2.3%	
MAFLD	4313	38.3%	877	33.5%	
No identifiable liver disease	2515	22.3%	370	14.1%	
Liver dysfunction					
Presence of hepatic encephalopathy	646	5.7%	169	6.5%	0.159
Presence of ascites	1159	10.3%	322	12.3%	0.003
Year of diagnosis					0.026
2001	537	4.8%	90	3.4%	
2002	608	5.4%	127	4.9%	
2003	574	5.1%	120	4.6%	
2004	659	5.9%	148	5.7%	
2005	652	5.8%	150	5.7%	
2006	637	5.7%	146	5.6%	
2007	712	6.3%	169	6.5%	
2008	742	6.6%	176	6.7%	
2009	777	6.9%	176	6.7%	
2010	814	7.2%	184	7.0%	
2011	868	7.7%	200	7.6%	
2012	908	8.1%	203	7.8%	
2013	912	8.1%	242	9.2%	
2014	931	8.3%	215	8.2%	
2015	926	8.2%	271	10.4%	

Supplemental Table 2: Odds of curative treatment receipt among patients with early-stage HCC.

	Base Model n=2457 OR (95% CI)	Low poverty Neighborhoods n=1092 OR (95% CI)	Moderate Poverty Neighborhoods n=765 OR (95% CI)	High poverty Neighborhoods n=600 OR (95% CI)
Age at diagnosis				
65 years – 69 years	Ref	Ref	Ref	Ref
70 years – 74 years	0.85 (0.68,1.06)	0.87 (0.62,1.22)	0.97 (0.63,1.50)	0.65 (0.42,1.01)
75 years – 79 years	0.63 (0.49,0.81)	0.65 (0.43,0.97)	0.72 (0.46,1.11)	0.49 (0.29,0.84)
80 years and over	0.44 (0.34,0.58)	0.41 (0.28,0.62)	0.58 (0.35,0.97)	0.33 (0.18,0.60)
Male	1.04 (0.86,1.25)	1.04 (0.78,1.37)	1.38 (0.98,1.94)	0.80 (0.54,1.19)
Race and ethnicity				
White	Ref	Ref	Ref	Ref
Black	0.94 (0.68,1.31)	1.35 (0.68,2.69)	1.24 (0.65,2.39)	0.66 (0.40,1.11)
Asian	1.05 (0.80,1.39)	0.96 (0.63,1.44)	1.23 (0.74,2.03)	1.30 (0.71,2.40)
Hispanic	0.97 (0.64,1.48)	0.58 (0.22,1.56)	0.73 (0.34,1.55)	1.92 (1.03,3.56)
Other/Unknown	1.31 (0.95,1.79)	1.45 (0.91,2.32)	1.94 (1.08,3.49)	0.64 (0.29,1.40)
Neighborhood-level SES				
Low poverty neighborhoods	Ref			
Moderate poverty neighborhoods	0.93 (0.75,1.15)			
High poverty neighborhoods	1.01 (0.77,1.34)			
Census tract education level	1.00 (0.99,1.01)	0.99 (0.97,1.01)	1.00 (0.99,1.01)	1.00 (0.99,1.02)
Geographic region				
West	Ref	Ref	Ref	Ref
Northeast	1.35 (1.03,1.76)	1.35 (0.96,1.91)	1.22 (0.71,2.10)	1.42 (0.63,3.22)
Midwest	1.08 (0.80,1.48)	1.07 (0.68,1.68)	1.00 (0.56,1.80)	1.94 (0.95,3.99)
South	0.99 (0.77,1.26)	0.76 (0.47,1.23)	1.21 (0.81,1.80)	1.21 (0.73,2.01)

NCI comorbidity index				
0	Ref	Ref	Ref	Ref
1	1.03 (0.75,1.42)	1.04 (0.64,1.68)	0.92 (0.51,1.68)	1.22 (0.62,2.37)
2	0.94 (0.70,1.26)	0.89 (0.57,1.39)	0.98 (0.56,1.71)	1.05 (0.56,1.97)
3	0.99 (0.74,1.32)	0.98 (0.63,1.52)	0.73 (0.42,1.26)	1.42 (0.75,2.66)
4	0.89 (0.59,1.34)	1.05 (0.56,1.94)	0.95 (0.48,1.92)	0.40 (0.16,1.02)
>=5	0.65 (0.48,0.89)	0.64 (0.39,1.04)	0.60 (0.34,1.08)	0.82 (0.43,1.56)
Liver disease etiology				
HCV	Ref	Ref	Ref	Ref
HBV	1.12 (0.79,1.59)	1.13 (0.67,1.91)	1.12 (0.59,2.15)	1.29 (0.60,2.74)
Alcohol related liver disease	0.59 (0.44,0.79)	0.51 (0.33,0.78)	0.98 (0.58,1.66)	0.42 (0.20,0.86)
Other liver disease	1.87 (1.05,3.33)	1.64 (0.80,3.40)	2.45 (0.71,8.52)	2.14 (0.49,9.33)
MAFLD	0.92 (0.74,1.16)	0.86 (0.61,1.21)	1.22 (0.82,1.82)	0.65 (0.40,1.05)
No identifiable liver disease	0.51 (0.37,0.71)	0.68 (0.41,1.11)	0.30 (0.15,0.60)	0.39 (0.20,0.76)
Liver dysfunction				
Presence of hepatic encephalopathy	0.77(0.57,1.06)	0.85(0.53,1.35)	0.80(0.45,1.41)	0.66(0.33,1.33)
Presence of ascites	1.05(0.81,1.36)	1.07(0.72,1.58)	1.29(0.80,2.07)	0.81(0.46,1.40)
Year of diagnosis				
2001	Ref	Ref	Ref	Ref
2002	0.66 (0.31,1.39)	0.55 (0.19,1.61)	1.10 (0.24,5.08)	1.07 (0.18,6.32)
2003	0.80 (0.38,1.66)	1.00 (0.36,2.79)	0.51 (0.12,2.19)	0.81 (0.10,6.22)
2004	0.61 (0.31,1.18)	0.49 (0.19,1.27)	0.57 (0.14,2.27)	1.40 (0.28,7.00)
2005	0.76 (0.37,1.52)	0.63 (0.21,1.86)	0.56 (0.14,2.25)	1.97 (0.40,9.67)
2006	0.75 (0.39,1.44)	0.88 (0.35,2.23)	0.49 (0.13,1.90)	1.22 (0.24,6.24)
2007	0.75 (0.39,1.44)	0.64 (0.25,1.67)	0.66 (0.17,2.57)	1.15 (0.24,5.46)
2008	0.83 (0.43,1.60)	0.99 (0.39,2.47)	0.51 (0.14,1.93)	1.04 (0.18,6.07)
2009	0.70 (0.37,1.33)	0.84 (0.33,2.14)	0.32 (0.08,1.17)	1.73 (0.38,8.00)
2010	0.62 (0.33,1.16)	0.68 (0.27,1.72)	0.53 (0.15,1.89)	0.69 (0.15,3.27)
2011	0.78 (0.41,1.47)	0.77 (0.30,1.96)	0.47 (0.13,1.73)	1.53 (0.34,6.79)
2012	0.74 (0.40,1.37)	0.69 (0.27,1.77)	0.45 (0.13,1.64)	1.43 (0.33,6.19)
2013	0.81 (0.44,1.52)	0.75 (0.30,1.89)	0.57 (0.16,2.02)	1.65 (0.38,7.30)
2014	0.65 (0.35,1.22)	0.57 (0.23,1.41)	0.57 (0.16,2.04)	1.02 (0.23,4.61)
2015	0.81 (0.44,1.48)	0.80 (0.33,1.94)	0.54 (0.15,1.92)	1.53 (0.35,6.63)

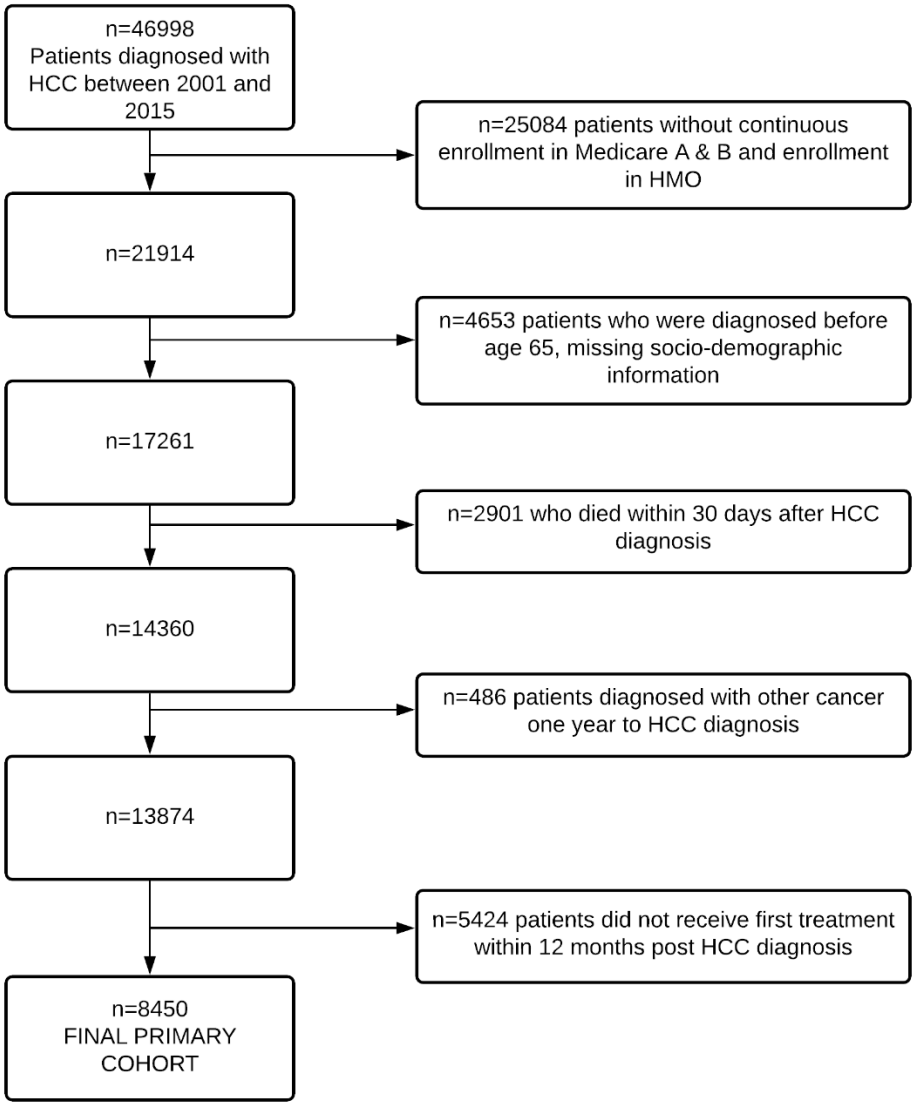
Supplemental Table 3: Predictors of overall survival among patients with early-stage HCC.

	Base Model n=2457 HR (95% CI)	Low poverty Neighborhoods n=1092 HR (95% CI)	Moderate Poverty Neighborhoods n=765 HR (95% CI)	High poverty Neighborhoods n=600 HR (95% CI)
Curative treatment				
Not received	Ref	Ref	Ref	Ref
Received	0.66 (0.60,0.72)	0.69 (0.60,0.80)	0.59 (0.49,0.70)	0.66 (0.54,0.81)
Age at diagnosis				
65 years – 69 years	Ref	Ref	Ref	Ref
70 years – 74 years	1.18 (1.04,1.35)	1.18 (0.96,1.45)	1.21 (0.95,1.55)	1.13 (0.88,1.45)
75 years – 79 years	1.48 (1.29,1.71)	1.66 (1.33,2.06)	1.67 (1.32,2.11)	1.06 (0.78,1.43)
80 years and over	1.79 (1.55,2.07)	1.86 (1.48,2.33)	1.95 (1.51,2.52)	1.55 (1.16,2.07)
Male	1.08(0.98,1.20)	1.14(0.98,1.34)	0.98(0.82,1.19)	1.17(0.95,1.44)
Race and ethnicity				
White	Ref	Ref	Ref	Ref
Black	1.15 (0.95,1.40)	0.97 (0.61,1.53)	1.38 (0.94,2.01)	1.14 (0.85,1.51)
Asian	0.68 (0.58,0.81)	0.72 (0.56,0.92)	0.67 (0.49,0.91)	0.59 (0.42,0.84)
Hispanic	0.92 (0.72,1.19)	0.85 (0.54,1.31)	1.24 (0.82,1.87)	0.73 (0.49,1.10)
Other/Unknown	0.78 (0.65,0.94)	0.70 (0.54,0.92)	0.86 (0.61,1.23)	0.71 (0.46,1.11)
Neighborhood-level SES				
Low poverty neighborhoods	Ref			
Moderate poverty neighborhoods	0.98 (0.87,1.10)			
High poverty neighborhoods	0.97 (0.83,1.14)			
Census tract education level	1.01 (1.00,1.01)	1.02 (1.01,1.02)	1.00 (1.00,1.01)	1.00 (1.00,1.01)
Geographic region				
West	Ref	Ref	Ref	Ref
Northeast	0.92 (0.79,1.07)	0.90 (0.74,1.10)	1.24 (0.95,1.62)	0.63 (0.40,1.00)
Midwest	1.03 (0.86,1.22)	1.03 (0.79,1.34)	1.05 (0.78,1.42)	0.86 (0.56,1.30)

South	1.07 (0.93,1.24)	1.10 (0.84,1.43)	1.03 (0.81,1.31)	
NCI comorbidity index				
0	Ref	Ref	Ref	Ref
1	0.92 (0.77,1.10)	0.89 (0.68,1.15)	1.09 (0.78,1.52)	0.73 (0.51,1.07)
2	0.92 (0.78,1.09)	0.92 (0.72,1.18)	1.06 (0.78,1.43)	0.71 (0.50,1.00)
3	0.97 (0.82,1.16)	1.11 (0.87,1.43)	0.99 (0.71,1.38)	0.67 (0.47,0.96)
4	1.14 (0.92,1.43)	0.97 (0.68,1.38)	1.59 (1.13,2.23)	0.88 (0.53,1.45)
>=5	1.19 (1.01,1.42)	1.13 (0.87,1.47)	1.47 (1.09,1.98)	0.94 (0.66,1.33)
Liver disease etiology				
HCV	Ref	Ref	Ref	Ref
HBV	0.70 (0.56,0.88)	0.65 (0.47,0.89)	0.91 (0.58,1.43)	0.60 (0.37,0.95)
Alcohol related liver disease	1.22 (1.04,1.44)	1.34 (1.05,1.70)	1.21 (0.90,1.63)	1.03 (0.73,1.44)
Other liver disease	0.71 (0.50,1.01)	0.74 (0.46,1.20)	0.95 (0.54,1.70)	0.40 (0.14,1.09)
MAFLD	1.04 (0.91,1.19)	0.94 (0.77,1.16)	1.18 (0.93,1.49)	1.08 (0.83,1.40)
No identifiable liver disease	1.07 (0.90,1.27)	1.08 (0.84,1.38)	1.29 (0.95,1.75)	0.82 (0.58,1.15)
Liver dysfunction				
Presence of hepatic encephalopathy	1.29 (1.08,1.53)	1.16 (0.90,1.49)	1.32 (0.95,1.84)	1.71 (1.20,2.44)
Presence of ascites	1.20 (1.03,1.39)	1.38 (1.11,1.72)	1.07 (0.81,1.40)	0.99 (0.72,1.35)

9. APPENDIX C

9.1. Supplemental Figures



Supplemental Figure 1. Sample flow.

9.2. Supplemental Tables

Supplemental Table 1. Correlates of overall survival – 5-month landmark in early-stage HCC (without and with type of first HCC treatment).

	Overall survival (Without first HCC treatment) n=1692 HR (95% CI)	Overall survival (with first HCC treatment) n=1692 HR (95% CI)
Delayed treatment	1.22 (1.02,1.46)	1.12 (0.93,1.35)
Age at diagnosis		
65 - 69 years	Ref	Ref
70 - 74 years	1.20 (1.02,1.41)	1.21 (1.03,1.42)
75 - 79 years	1.40 (1.18,1.67)	1.35 (1.14,1.61)
80 years and older	1.70 (1.42,2.05)	1.56 (1.29,1.87)
Male	1.18 (1.04,1.35)	1.20 (1.06,1.37)
Race and ethnicity		
White	Ref	Ref
Black	1.48 (0.84,2.62)	1.59 (0.87,2.91)
Asian	0.80 (0.61,1.05)	0.82 (0.62,1.08)
Hispanic	0.87 (0.52,1.46)	0.85 (0.52,1.39)
Other/Unknown	0.61 (0.43,0.86)	0.68 (0.48,0.97)
Neighborhood-level SES		
Low poverty neighborhoods	Ref	Ref
Moderate poverty neighborhoods	0.97 (0.81,1.16)	0.95 (0.79,1.13)
High poverty neighborhoods	1.11 (0.89,1.37)	1.07 (0.86,1.33)
Interaction of race, ethnicity, and poverty		
Black#Moderate poverty neighborhoods	0.76 (0.38,1.53)	0.72 (0.35,1.46)
Black#Poor neighborhoods	0.85 (0.44,1.65)	0.73 (0.37,1.45)
Asian#Moderate poverty neighborhoods	0.77 (0.50,1.17)	0.81 (0.53,1.23)
Asian#Poor neighborhoods	0.88 (0.57,1.38)	0.86 (0.55,1.36)
Hispanic#Moderate poverty neighborhoods	1.60 (0.76,3.36)	1.58 (0.76,3.31)
Hispanic#Poor neighborhoods	0.74 (0.36,1.50)	0.75 (0.38,1.51)
Geographic region		
West	Ref	Ref
Northeast	0.90 (0.74,1.09)	0.95 (0.78,1.15)
Midwest	1.14 (0.92,1.43)	1.14 (0.91,1.42)
South	1.03 (0.86,1.24)	1.13 (0.93,1.37)
Metropolitan status	Ref	Ref
Metro > 1 million	1.06 (0.90,1.24)	1.05 (0.90,1.24)
Metro 250,000 - 1 million	1.15 (0.90,1.48)	1.16 (0.89,1.51)
Metro <250,000	0.95 (0.76,1.20)	0.95 (0.76,1.20)
Non-Metro		

NCI comorbidity index		
0	Ref	Ref
1	0.93 (0.74,1.18)	0.95 (0.75,1.19)
2	1.05 (0.85,1.31)	1.04 (0.83,1.29)
3	1.11 (0.89,1.39)	1.08 (0.86,1.35)
4	1.20 (0.89,1.61)	1.14 (0.85,1.54)
>=5	1.34 (1.05,1.72)	1.32 (1.03,1.70)
Liver disease etiology		
HCV	Ref	Ref
HBV	0.68 (0.52,0.89)	0.71 (0.54,0.94)
Alcohol related liver disease	1.25 (1.02,1.53)	1.30 (1.07,1.60)
Other liver diseases	0.64 (0.42,0.95)	0.67 (0.43,1.02)
MAFLD	0.96 (0.81,1.13)	1.05 (0.89,1.24)
No identifiable liver disease	1.03 (0.81,1.31)	1.16 (0.90,1.48)
Liver dysfunction		
Presence of hepatic encephalopathy	1.32 (1.05,1.66)	1.34 (1.06,1.68)
Presence of ascites	1.19 (0.99,1.44)	1.10 (0.91,1.33)
First HCC treatment type		
Liver transplantation		0.37 (0.24,0.56)
Surgical resection		0.50 (0.41,0.61)
Local ablation		0.91 (0.79,1.05)
Embolization		Ref
Systemic chemotherapy		1.16 (0.90,1.50)
Radiation		1.55 (1.08,2.23)

Supplemental Table 2. Correlates of overall survival – 5-month landmark in advanced stage HCC (without and with type of first HCC treatment).

	Overall survival (Without first HCC treatment) n=3391 HR (95% CI)	Overall survival (with first HCC treatment) n=3391 HR (95% CI)
Delayed treatment	1.22 (1.09,1.37)	1.16 (1.03,1.30)
Age at diagnosis		
65 - 69 years	Ref	Ref
70 - 74 years	1.23 (1.10,1.37)	1.23 (1.10,1.38)
75 - 79 years	1.42 (1.27,1.59)	1.37 (1.22,1.54)
80 years and older	1.52 (1.36,1.71)	1.44 (1.28,1.62)
Male	1.10 (1.01,1.20)	1.06 (0.97,1.15)
Race and ethnicity		
White	Ref	Ref
Black	0.99 (0.69,1.41)	0.89 (0.60,1.30)
Asian	0.82 (0.69,0.97)	0.76 (0.63,0.91)
Hispanic	1.49 (1.01,2.20)	1.44 (0.99,2.09)
Other/Unknown	0.80 (0.64,1.00)	0.81 (0.65,1.02)
Neighborhood-level SES		
Low poverty neighborhoods	Ref	Ref
Moderate poverty neighborhoods	1.01 (0.91,1.13)	0.99 (0.89,1.10)
High poverty neighborhoods	1.16 (1.01,1.32)	1.08 (0.94,1.24)
Interaction of race, ethnicity, and poverty		
Black#Moderate poverty neighborhoods	1.00 (0.64,1.55)	1.03 (0.64,1.63)
Black#Poor neighborhoods	1.06 (0.69,1.61)	1.15 (0.73,1.80)
Asian#Moderate poverty neighborhoods	1.26 (0.98,1.62)	1.38 (1.07,1.78)
Asian#Poor neighborhoods	0.87 (0.64,1.19)	0.91 (0.65,1.26)
Hispanic#Moderate poverty neighborhoods	1.08 (0.67,1.73)	1.09 (0.69,1.71)
Hispanic#Poor neighborhoods	0.73 (0.45,1.19)	0.75 (0.47,1.20)
Other/unknown#Moderate poverty neighborhoods	1.04 (0.72,1.49)	0.94 (0.65,1.37)
Other/unknown#Poor neighborhoods	0.99 (0.66,1.49)	1.04 (0.68,1.57)
Geographic region		
West	Ref	Ref
Northeast	0.98 (0.88,1.09)	1.02 (0.91,1.14)
Midwest	1.16 (1.00,1.33)	1.14 (0.98,1.32)
South	1.08 (0.96,1.22)	1.18 (1.04,1.34)

Metropolitan status		
Metro > 1 million	Ref	Ref
Metro 250,000 - 1 million	1.08 (0.98,1.19)	1.08 (0.98,1.19)
Metro <250,000	0.96 (0.82,1.11)	0.92 (0.78,1.07)
Non-Metro	0.87 (0.76,1.00)	0.87 (0.76,1.00)
NCI comorbidity index		
0	Ref	Ref
1	1.06 (0.95,1.20)	1.08 (0.96,1.22)
2	1.00 (0.88,1.13)	1.01 (0.89,1.15)
3	1.11 (0.98,1.26)	1.13 (0.99,1.30)
4	1.24 (1.05,1.47)	1.25 (1.05,1.49)
>=5	1.28 (1.10,1.49)	1.28 (1.09,1.50)
Liver disease etiology		
HCV	Ref	Ref
HBV	0.75 (0.61,0.91)	0.82 (0.67,1.00)
Alcohol related liver disease	1.03 (0.88,1.19)	1.01 (0.87,1.17)
Other liver diseases	1.19 (0.91,1.56)	1.26 (0.97,1.63)
MAFLD	1.00 (0.91,1.11)	1.03 (0.93,1.14)
No identifiable liver disease	1.18 (1.03,1.34)	1.25 (1.08,1.43)
Liver dysfunction		
Presence of hepatic encephalopathy	1.00 (0.82,1.22)	1.04 (0.86,1.26)
Presence of ascites	1.14 (0.99,1.32)	1.06 (0.91,1.23)
First HCC treatment type		
Embolization		Ref
Liver transplantation		0.28 (0.19,0.41)
Surgical resection		0.48 (0.42,0.54)
Local ablation		0.77 (0.69,0.87)
Systemic chemotherapy		1.53 (1.37,1.69)
Radiation		1.74 (1.39,2.17)

Supplemental Table 3. Correlates of overall survival – 5-month landmark in patients who received curative treatment (without and with type of first HCC treatment).

	Overall survival (Without first HCC treatment) n=2254 HR (95% CI)	Overall survival (with first HCC treatment) n=2254 HR (95% CI)
Delayed treatment	1.24 (1.04,1.48)	1.13 (0.94,1.35)
Age at diagnosis		
65 - 69 years	Ref	Ref
70 - 74 years	1.01 (0.88,1.17)	0.95 (0.82,1.09)
75 - 79 years	1.35 (1.17,1.56)	1.20 (1.04,1.39)
80 years and older	1.59 (1.36,1.85)	1.39 (1.18,1.62)
Male	1.10 (0.98,1.23)	1.11 (0.99,1.24)
Race and ethnicity		
White	Ref	Ref
Black	1.05 (0.66,1.68)	1.02 (0.62,1.71)
Asian	0.94 (0.75,1.17)	0.95 (0.77,1.19)
Hispanic	1.08 (0.59,1.98)	1.07 (0.59,1.92)
Other/Unknown	0.70 (0.53,0.94)	0.73 (0.55,0.98)
Neighborhood-level SES		
Low poverty neighborhoods	Ref	Ref
Moderate poverty neighborhoods	0.91 (0.77,1.06)	0.93 (0.80,1.09)
High poverty neighborhoods	1.07 (0.89,1.29)	1.12 (0.93,1.35)
Interaction of race, ethnicity, and poverty		
Black#Moderate poverty neighborhoods	1.08 (0.60,1.94)	1.05 (0.57,1.96)
Black#Poor neighborhoods	1.30 (0.75,2.24)	1.14 (0.64,2.03)
Asian#Moderate poverty neighborhoods	0.77 (0.54,1.10)	0.72 (0.50,1.03)
Asian#Poor neighborhoods	0.80 (0.53,1.20)	0.82 (0.54,1.24)
Hispanic#Moderate poverty neighborhoods	1.21 (0.55,2.650	1.13 (0.53,2.41)
Hispanic#Poor neighborhoods	0.91 (0.43,1.91)	0.91 (0.45,1.85)
Other/unknown#Moderate poverty neighborhoods	1.51 (0.95,2.39)	1.27 (0.78,2.06)
Other/unknown#Poor neighborhoods	1.28 (0.79,2.07)	1.18 (0.72,1.95)
Geographic region		
West	Ref	Ref
Northeast	1.04 (0.90,1.21)	1.05 (0.91,1.21)
Midwest	1.21 (0.99,1.48)	1.24 (1.02,1.52)
South	1.15 (0.98,1.34)	1.26 (1.08,1.47)
Metropolitan status		
Metro > 1 million	Ref	Ref
Metro 250,000 - 1 million	1.12 (0.98,1.28)	1.12 (0.97,1.28)
Metro <250,000	1.24 (1.01,1.53)	1.20 (0.97,1.49)
Non-Metro	0.93 (0.77,1.13)	0.94 (0.78,1.14)

Tumor Staging		
Unifocal <=5 cm without vascular invasion and metastasis	Ref	Ref
Beyond unifocal without vascular invasion and metastasis	1.18 (1.05,1.33)	1.26 (1.12,1.42)
Vascular invasion or metastasis	1.87 (1.49,2.34)	2.21 (1.78,2.76)
Non-determinable	1.56 (1.34,1.82)	1.75 (1.50,2.05)
NCI comorbidity index		
0	Ref	Ref
1	0.98 (0.84,1.15)	0.96 (0.82,1.13)
2	1.12 (0.95,1.33)	1.07 (0.90,1.27)
3	1.16 (0.96,1.38)	1.15 (0.96,1.38)
4	1.52 (1.20,1.91)	1.47 (1.17,1.85)
>=5	1.27 (1.03,1.57)	1.24 (1.01,1.53)
Liver disease etiology		
HCV	Ref	Ref
HBV	0.65 (0.51,0.82)	0.67 (0.52,0.85)
Alcohol related liver disease	0.92 (0.74,1.14)	0.98 (0.80,1.20)
Other liver diseases	0.73 (0.50,1.08)	0.81 (0.55,1.20)
MAFLD	0.80 (0.70,0.91)	0.86 (0.75,0.99)
No identifiable liver disease	0.88 (0.74,1.05)	0.93 (0.77,1.11)
Liver dysfunction		
Presence of hepatic encephalopathy	0.91 (0.69,1.21)	1.03 (0.77,1.37)
Presence of ascites	1.30 (1.04,1.62)	1.27 (1.02,1.59)
First HCC treatment type		
Liver transplantation		Ref
Surgical resection		1.94 (1.43,2.63)
Local ablation		3.08 (2.30,4.14)