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Racial, Ethnic, and Socioeconomic Disparities in Treatment Delay among Patients with Hepatocellular Carcinoma in the United States

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Abstract

Background: Failures have been reported across the cancer care continuum in patients with hepatocellular carcinoma (HCC); however, the impact of treatment delays on outcomes has not been well characterized. We described the prevalence of treatment delays in a racially and ethnically diverse cohort of patients and its association with overall survival.

Methods: Using the Surveillance, Epidemiology, and End Results (SEER) – Medicare database, we identified patients diagnosed with HCC between 2001 and 2015. We performed multivariable logistic regression analysis to identify factors associated with treatment delay, i.e., receipt of HCC-directed therapy > three months after diagnosis. Cox proportional hazards regression analysis with a 5-month landmark was used to characterize the association between treatment delay and overall survival, accounting for immortal time bias.

Results: Of 8450 patients with treatment within 12 months of HCC diagnosis, 1205 (14.3%) experienced treatment delays. The proportion with treatment delays ranged from 6.8% of patients

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Disclosures

Amit Singal has served as a consultant or on advisory boards for Bayer, Eisai, BMS, Exelixis, Genentech, AstraZeneca, FuijFilm Medical Sciences, Exact Sciences, Roche, Glycotest, GRAIL, and TARGET RWE.

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undergoing surgical resection to 21.6% of those undergoing liver transplantation. In multivariable analysis, Black patients (OR 1.96, 95%CI 1.21 – 3.15) and those living in high poverty neighborhoods (OR 1.55, 95%CI 1.25 – 1.92) were more likely to experience treatment delays than White patients and those living in low poverty neighborhoods, respectively. Treatment delay was independently associated with worse survival (HR 1.15 95%CI 1.05 – 1.25).

Conclusion: Nearly one in seven patients with HCC experience treatment delays, with higher odds in Black patients and those living in high poverty neighborhoods. Treatment delays are associated with worse survival, highlighting a need for interventions to improve time-to-treatment.

Keywords

Treatment; prognosis; survival; inequity; liver cancer

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.[1] With increased hepatitis B vaccination and hepatitis C treatment uptake, viral-related HCC is decreasing. 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.[2]

Despite advances in treatment options, the 5-year survival for HCC remains poor at less than 20%.[3] This poor prognosis is partly related to failures across the cancer care continuum, with demonstrated underuse of HCC screening and treatment.[4–7] 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.[8–10] However, few studies have characterized the prevalence of treatment delays and the potential association with survival in large, racially, and socioeconomically diverse populations.[11,12] These data are important as studies in breast and colorectal cancers have demonstrated that treatment delays are common and associated with worse survival.[13–15] 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.[16]

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.

METHODS

Data source and Study population

The 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.[17] We included Medicare beneficiaries aged ≥65 years 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.[18] 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) enrolled in health maintenance organizations[17,19]; (3) 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 HCC treatment (Supplemental Figure).[19] This study protocol was deemed exempt by the IRB at Texas A&M University.

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).[20–22] 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 previously described.[23] We conducted a sensitivity analysis using SEER stage, classified as localized, regional, or distant. In addition, we abstracted 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-associated liver disease, other liver diseases, 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.[24,25]

Outcomes and Statistical analysis

Our primary outcome 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.[6,12,26,27] HCC-specific treatments were abstracted from Medicare claims data using the ICD-9, ICD-10-Procedure Coding System, HCPCS, and CPT codes within 12 months post HCC diagnosis. HCC treatments were categorized into the most definitive treatment, defined hierarchically as liver transplantation, surgical resection, local ablation, transarterial embolization, external radiation, and systemic therapy. For patients who underwent liver transplantation, those who received bridging therapy within 3 months while awaiting transplant were considered to have received timely treatment. Chi-square tests were used to compare patient characteristics between those who received timely treatment (i.e., ≤3 months) versus delayed treatment (i.e., >3 months). Variables associated with delays were (p<0.10) were included in multivariable analysis. Factors of known clinical significance, e.g., liver dysfunction and sex,

were selected *a priori*. We 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.[28,29] We used landmark analysis instead of time-dependent Cox regression analyses given our aim was to evaluate if timely treatment, instead of simply receipt of treatment, was associated with survival.[30,31] Survival was defined from the time of the landmark to death from any cause. A landmark of 5 months was selected for the primary analysis based on prior literature and tumor doubling times.[26,27] Patients whose HCC was treated within 3 months were classified as timely treatment, therapy between 4–5 months as delayed treatment, and those with therapy beyond 5 months were excluded. Patients who died prior to the 5-month landmark were also excluded. 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. We conducted post-hoc sensitivity analyses using 6-, 7-, 8- and 9-month landmarks. We also conducted a post-hoc sensitivity analysis excluding patients who underwent liver transplantation as first therapy given anticipated wait times before being awarded MELD exception points.

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).

RESULTS

Patient characteristics

Of 13,874 patients with HCC, 8,450 (60.9%) were treated within 12 months of diagnosis (Supplemental Figure 1). 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 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.

Prevalence and Correlates of Treatment delay

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 1). Characteristics of patients receiving timely versus delayed treatment are shown in Table 1. 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 HCC therapy, with the highest delays observed in patients who underwent liver transplantation and lowest in

those treated with surgical resection (Figure 2 and Supplemental Table 1). Among 480 patients who underwent transplantation over a time horizon of 56 months, 327 (68.1%) had prior bridging therapy, with 285 (87.1%) doing so within 3 months. Of 153 patients who underwent transplantation as initial treatment, 120 (78.3%) did so within 3 months of 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 2), we continued to observe sociodemographic disparities in treatment delays. Specifically, Black patients (OR 1.91 95%CI 1.20 – 3.05) and patients in moderate-high poverty neighborhoods (moderate poverty: OR 1.30 95%CI 1.08 – 1.57; high poverty: 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.

Overall survival

In the 5-month landmark analysis (n=6644), 5954 patients (89.6%) received timely treatment while 690 patients (10.4%) received delayed treatment. Median overall survival of the cohort was 25 (IQR 11 to 61) months – 25 months for patients with timely treatment versus 23 months for those with treatment delay. Treatment delay was associated with worse survival in univariable (HR 1.13 95% CI 1.04 – 1.23) (Figure 3) and multivariable (HR 1.15, 95%CI 1.05 – 1.25) analyses. In multivariable analysis, compared to White patients, Hispanic patients had worse survival (HR 1.40 95%CI 1.08 – 1.82), whereas Asian patients had better survival (HR 0.82 95% CI 0.73 – 0.93). There was no significant difference in survival between Black patients and White patients. Median overall survival was 35 months for Asian patients compared to 23, 22, and 20 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 type of HCC treatment was added to the model, treatment delay was not associated with worse survival (Table 3).

In subgroup analyses by tumor stage (Supplemental Table 2 and 3), treatment delay was associated with worse survival for patients with early-stage HCC (HR 1.21 95%CI 1.02 – 1.44), although this was no longer significant when type of HCC treatment was added to the model (HR 1.11 95%CI 0.92 – 1.33). In non-early-stage patients, treatment delay was associated with higher mortality in both models (Supplemental Table 3). We also conducted subgroup analyses by curative (i.e., transplantation, resection, local ablation) vs. non-curative treatment (i.e., transarterial embolization, radiation, and systemic therapy). Delayed treatment was associated with worse survival among patients who received curative treatment, although this association was mitigated when type of HCC treatment was added to the model (Supplemental Table 4). For non-curative treatments, delayed

treatment was not associated with overall survival in either model (Supplemental Table 5). Sensitivity analyses using SEER staging (i.e., local, regional, distant) yielded similar results. In sensitivity analyses using 6-, 7-, 8- and 9-month landmarks, delayed treatment continued to be associated with worse overall survival (Supplemental Table 6). Results were unchanged when excluding patients who underwent liver transplantation as their first therapy (Supplemental Table 7).

DISCUSSION

In this population-based sample, we found 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 survival, highlighting a need for interventions to improve time-to-treatment for patients with HCC.

Prior studies have described racial and socioeconomic disparities in HCC treatment utilization and overall survival.[4,32,33] In a 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.[23] The current study extends this work by demonstrating racial and ethnic disparities in treatment delays and survival even in a selected population of Medicare beneficiaries. Further, our findings are consistent with a study in the VA system; taken together these data indicate that insurance status alone cannot account for observed disparities in HCC outcomes.[34] This is consistent with prior studies that demonstrated significant racial and ethnic disparities among Medicare enrollees in adverse health indicators, timely cancer screening, and in the patient experience of care coordination.[35–37] This persistent disparity may be 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.[38]

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 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.[39,40] There are also 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.[41,42] 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[43]. On a broad scale, some inequities observed in this population can be attributed to structural socioeconomic and environmental factors rooted in discrimination and systemic racism.[44] 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.[37] Prior studies have also demonstrated wide variability in racial and ethnic disparities in the Medicare population across regions and for different procedures.[45] 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.[46]

In our 5-month landmark analysis accounting for immortal time bias, we found HCC treatment delay was associated with worse survival although the difference was no longer statistically significant after type of first treatment was added to the model. Longer delayed treatments of 7 months or greater continued to be associated with worse survival in models with and without type of first treatment. Our findings are consistent with prior studies examining the impact of treatment delay on survival in other cancers, including breast and colorectal cancer.[13–15,48,49] Prior studies in HCC have reported discordant findings regarding the association between treatment delays and survival.[6,12,47] This discordance may be partly related to specific reasons for treatment delay and 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, including those who are listed for liver transplantation.

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.[50] However, we acknowledge 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 generalizability of the findings.[17] Additionally, SEER-Medicare does not have sufficiently granular data to assess robust parameters of liver dysfunction like Child-Pugh score, or validated predictors of survival in patients with cirrhosis like MELD score, or tumor characteristics to determine Milan Criteria or BCLC staging. Furthermore, although use of landmark analysis can best estimate the association of treatment receipt at a certain time (i.e., timely vs delayed treatment), it cannot fully address all inherent biases of a nonrandomized comparison.[29] However, our conclusions are strengthened by consistency across sensitivity analyses. 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.[50]

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing statement

"The data underlying this article cannot be shared publicly because the National Cancer Institute does not permit others to use the data except for collaborators at our institution involved with this research as described in our research proposal. However, this data can be obtained through https://healthcaredelivery.cancer.gov/seermedicare/obtain/ by paying the cost mentioned."

Abbreviations

CPL	Census tract poverty level
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HR	hazard ratio
HCC	Hepatocellular carcinoma
ICD-9	International Classification of Diseases, 9th revision
ICD-10	International Classification of Diseases, 10th revision
MAFLD	Metabolic Associated Liver Disease
NCI	National Cancer Institute
OR	odds ratio
SEER	Surveillance, Epidemiology and End Results
SES	Socioeconomic status

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What You Need to Know

Background

Treatment delays are common and associated with worse survival in several cancers; however, the prevalence and clinical significance of treatment delays in patients with hepatocellular carcinoma (HCC) have not been well characterized in large, diverse patient populations.

Findings

Using the SEER-Medicare database, we found nearly one in seven patients with HCC experience treatment delays exceeding 3 months. Black patients and those living in moderate or high poverty neighborhoods were more likely to experience treatment delays than White patients and those living in low poverty neighborhoods, respectively. Treatment delay was significantly associated with worse overall survival.

Implications

Racial and socioeconomic disparities in timely treatment may partly explain observed disparities in HCC clinical outcomes. Our findings highlight an urgent need for interventions to improve time-to-treatment for patients with HCC.

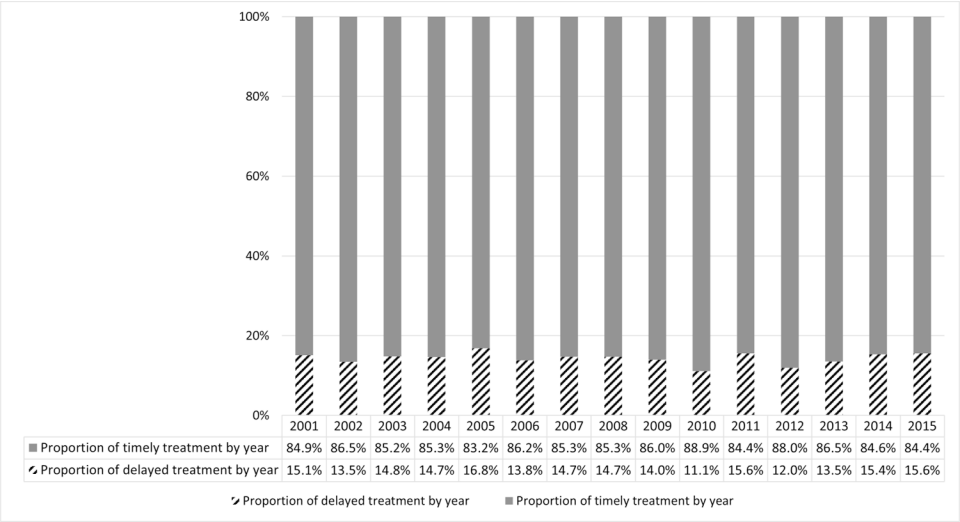

Figure 1.
Proportion of patients with delayed vs. timely HCC treatment over time

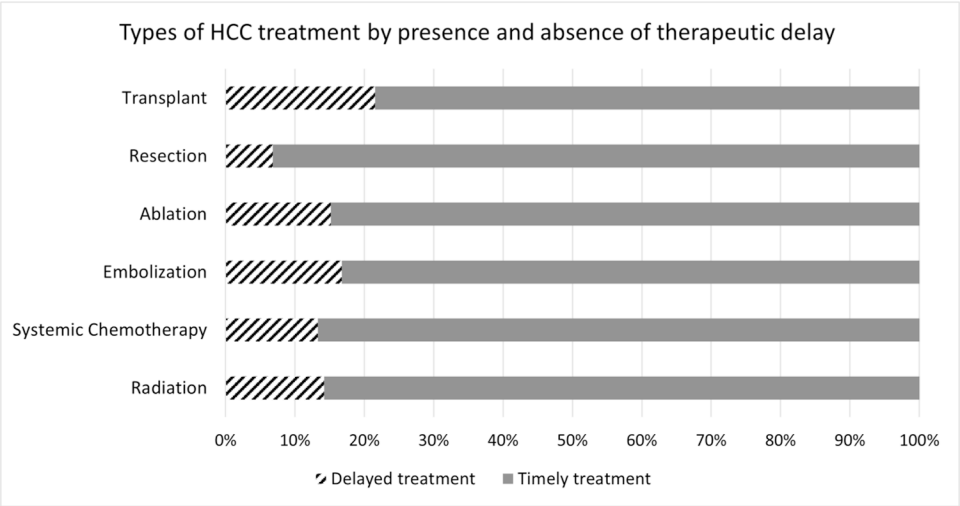

Figure 2.
Type of HCC treatment, by presence and absence of treatment delay

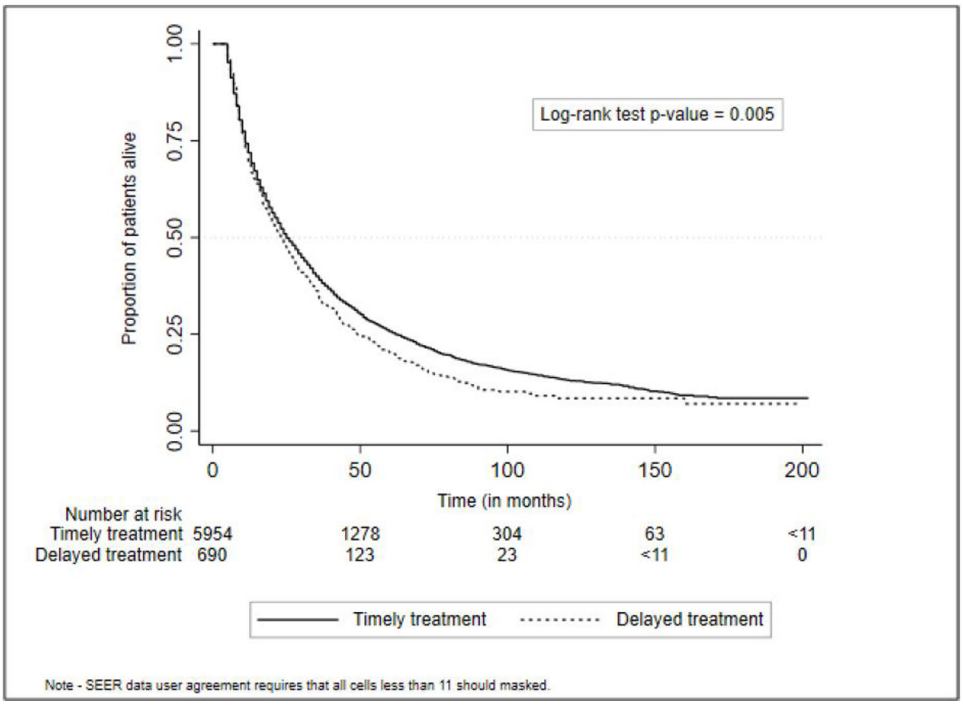

Figure 3.
Delayed treatment is associated with worse survival

Table 1.

Patient characteristics by presence or absence of treatment delay

	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					
65 – 69 years	1940	26.8%	390	32.4%	
70 – 74 years	2065	28.5%	369	30.6%	<0.001
75 – 79 years	1727	23.8%	232	19.3%	
80 years and older	1513	20.9%	214	17.8%	
Gender					
Female	2382	32.9%	393	32.6%	0.86
Male	4863	67.1%	812	67.4%	
Race and ethnicity					
White	4986	68.8%	771	64.0%	
Black	498	6.9%	124	10.3%	<0.001
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					
Low poverty neighborhoods	3558	49.1%	518	43.0%	<0.001
Moderate poverty neighborhoods	2093	28.9%	381	31.6%	
High poverty neighborhoods	1594	22.0%	306	25.4%	
Geographic region					
Northeast	1338	18.5%	228	18.9%	
West	3792	52.3%	696	57.8%	<0.001
Midwest	691	9.5%	101	8.4%	
South	1424	19.7%	180	14.9%	
Metropolitan status					
Metro > 1 million	4549	62.8%	750	62.2%	
Metro 250,000 – 1 million	1415	19.5%	255	21.2%	0.02
Metro <250,000	522	7.2%	103	8.5%	
Non-Metro	759	10.5%	97	8.0%	
Tumor Staging					
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%	<0.001
Non-determinable	1685	23.3%	204	16.9%	
SEER stage					
Localized	4531	62.5%	751	62.3%	

	Patients receiving timely treatment n=7245		Patients receiving delayed treatment n=1205		*P*-value
	n	%	n	%	
Regional	1753	24.2%	298	24.7%	0.01
Distant	766	10.6%	90	7.5%	
Unknown	375	5.2%	66	5.5%	
NCI comorbidity index					
0	1566	21.6%	237	19.7%	
1	1601	22.1%	218	18.1%	
2	1422	19.6%	245	20.3%	0.001
3	1315	18.2%	259	21.5%	
4	405	5.6%	85	7.1%	
>=5	936	12.9%	161	13.4%	
Liver disease etiology					
HCV	2175	30.0%	448	37.2%	
HBV	402	5.5%	59	4.9%	
Alcohol related liver disease	737	10.2%	137	11.4%	<0.001
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

Table 2.

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

	Delayed treatment (without first HCC treatment) n=8450 OR (95% CI)[1]	Delayed treatment (with first HCC treatment) n=8450 OR (95% CI)[2]
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)
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)

	Delayed treatment (without first HCC treatment) n=8450 OR (95% CI)[1]	Delayed treatment (with first HCC treatment) n=8450 OR (95% CI)[2]
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)
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)

[1]Model included year fixed effects (not reported)

[2]Model included year fixed effects (not reported)

Table 3.

Correlates of overall survival – 5-month landmark (without and with type of first HCC treatment)

	Overall survival (Without first HCC treatment) n=6644 HR (95% CI)	Overall survival (with first HCC treatment) n=6644 HR (95% CI)
Delayed treatment	1.15 (1.05,1.25)	1.07 (0.98,1.17)
Age at diagnosis		
65 – 69 years	Ref	Ref
70 – 74 years	1.15 (1.06,1.24)	1.16 (1.07,1.25)
75 – 79 years	1.31 (1.21,1.41)	1.25 (1.16,1.36)
80 years and older	1.44 (1.33,1.57)	1.36 (1.25,1.48)
Male	1.13 (1.06,1.20)	1.10 (1.04,1.18)
Race and ethnicity		
White	Ref	Ref
Black	0.84 (0.63,1.11)	0.79 (0.58,1.07)
Asian	0.83 (0.73,0.93)	0.79 (0.69,0.90)
Hispanic	1.40 (1.08,1.82)	1.32 (1.03,1.69)
Other/Unknown	0.75 (0.64,0.89)	0.78 (0.66,0.92)
Neighborhood-level SES		
Low poverty neighborhoods	Ref	Ref
Moderate poverty neighborhoods	1.04 (0.96,1.12)	1.02 (0.94,1.10)
High poverty neighborhoods	1.07 (0.97,1.18)	1.02 (0.92,1.13)
Interaction of race, ethnicity, and poverty		
Black#Moderate poverty neighborhoods	1.17 (0.83,1.64)	1.19 (0.83,1.70)
Black#High poverty neighborhoods	1.33 (0.96,1.84)	1.31 (0.93,1.86)
Asian#Moderate poverty neighborhoods	0.99 (0.83,1.19)	1.05 (0.87,1.27)
Asian#High poverty neighborhoods	0.93 (0.75,1.16)	0.97 (0.77,1.23)
Hispanic#Moderate poverty neighborhoods	0.94 (0.67,1.32)	0.96 (0.69,1.33)
Hispanic#High poverty neighborhoods	0.72 (0.51,1.01)	0.72 (0.52,1.01)
Geographic region		
West	Ref	Ref
Northeast	0.94 (0.87,1.01)	0.97 (0.90,1.05)
Midwest	1.10 (0.99,1.22)	1.12 (1.01,1.25)
South	1.08 (0.99,1.18)	1.16 (1.06,1.27)
Metropolitan status		
Metro > 1 million	Ref	Ref
Metro 250,000 – 1 million	1.03 (0.96,1.11)	1.03 (0.96,1.10)
Metro <250,000	1.02 (0.91,1.15)	0.99 (0.87,1.11)
Non-Metro	0.92 (0.83,1.03)	0.93 (0.83,1.04)
Tumor Staging		
Unifocal <=5 cm without vascular invasion and metastasis	Ref	Ref
Beyond unifocal without vascular invasion and metastasis	1.58 (1.47,1.69)	1.46 (1.36,1.57)

	Overall survival (Without first HCC treatment) n=6644 HR (95% CI)	Overall survival (with first HCC treatment) n=6644 HR (95% CI)
Vascular invasion or metastasis	2.16 (1.87,2.49)	2.15 (1.84,2.52)
Non-determinable	1.96 (1.80,2.14)	1.83 (1.68,2.00)
NCI comorbidity index		
0	Ref	Ref
1	1.04 (0.95,1.13)	1.04 (0.95,1.14)
2	1.02 (0.93,1.12)	1.03 (0.93,1.13)
3	1.07 (0.97,1.17)	1.08 (0.98,1.19)
4	1.20 (1.06,1.36)	1.14 (0.99,1.31)
>=5	1.27 (1.14,1.42)	1.22 (1.09,1.37)
Liver disease etiology		
HCV	Ref	Ref
HBV	0.68 (0.60,0.78)	0.72 (0.62,0.82)
Alcohol related liver disease	1.06 (0.96,1.18)	1.05 (0.95,1.16)
Other liver diseases	0.90 (0.74,1.10)	0.96 (0.79,1.17)
MAFLD	1.01 (0.93,1.08)	1.04 (0.97,1.12)
No identifiable liver disease	1.06 (0.96,1.17)	1.12 (1.01,1.24)
Liver dysfunction		
Presence of hepatic encephalopathy	1.06 (0.93,1.21)	1.08 (0.95,1.23)
Presence of ascites	1.15 (1.04,1.27)	1.07 (0.96,1.18)
First HCC treatment type		
Liver transplantation		0.33 (0.26,0.43)
Surgical resection		0.49 (0.45,0.53)
Local ablation		0.82 (0.76,0.89)
Embolization		Ref
Systemic chemotherapy		1.56 (1.44,1.69)
Radiation		1.56 (1.34,1.82)