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Disparities in Treatment and Survival in Early-Stage Hepatocellular Carcinoma in California

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Abstract

Background and Objectives—Curative intent therapy is the standard of care for early-stage hepatocellular carcinoma (HCC). However, these therapies are under-utilized, with several treatment and survival disparities. We sought to demonstrate whether type of facility and distance from treatment center (with transplant capabilities) contributed to disparities in curative-intent treatment and survival for early-stage HCC in California.

Methods—We performed a retrospective analysis of the California Cancer Registry (CCR) for patients diagnosed with stage I or II primary HCC between 2005 and 2017. Primary and

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secondary outcomes were receipt of treatment and overall survival, respectively. Multivariable logistic regression and Multivariable Cox proportional hazards regression were used to evaluate associations.

Results—Of 19,059 patients with early-stage HCC, only 36% (6,778) received curative-intent treatment. Compared to non-Hispanic White patients, Hispanic patients were less likely, and Asian/Pacific Islander patients were more likely to receive curative-intent treatment. Our results showed that rural residence, public insurance, lower neighborhood SES, and care at non-NCI designated cancer center were associated with not receiving treatment and decreased survival.

Conclusions: Although multiple factors influence receipt of treatment for early-HCC, our findings suggest that early intervention programs should target travel barriers and access to specialist care to help improve oncologic outcomes.

Keywords

Hepatocellular Carcinoma; Treatment; Disparities; NCI designated Center; Trans-plant Center; California

Introduction

Despite advancements in screening and treatment for hepatocellular carcinoma (HCC), overall 5-year survival remains poor at approximately 20%.[1] According to the National Comprehensive Cancer Network guidelines for HCC treatment, patients with potentially curative disease should be offered surgical resection, locoregional therapies or liver transplant as curative-intent therapy.[2] Despite that early stage HCC represents a population of patients who have the highest potential for cure, nationwide population-based research demonstrates broad underutilization and well documented disparities in treatments offered for these patients.[3–6] The disparities in receiving curative-intent treatment have been demonstrated with regards to race/ethnicity[7], insurance coverage[8], resident location[9], and specialization of treating facility.[10] Furthermore, type of hospital and hospital volume have been shown to affect the receipt of treatment, amplifying the end effects on overall early-stage HCC survival. Specifically, some studies have shown that hospital volume appears to outweigh the inconvenience of longer travel distances.[11]

In California, significant disparities in early-stage HCC incidence and treatment have been well documented in racial/ethnic minority populations[12,13] and those with lower socioeconomic status or who lack health insurance.[14,15] However, the impact of travel distance to transplant center and type of center (NCI-designation versus not) on utilization in curative-intent treatment and survival of early-stage HCC patients in California has not been evaluated. We sought to demonstrate whether treatment facility type and distance from treatment center with transplant capabilities play a role in disparities in curative-intent treatment and survival for early-stage HCC in California. We hypothesized that patients with access to an NCI-designated center and shorter travel distance to a transplant center would have higher odds of receiving curative-intent treatment with associated improved overall survival, potentially exposing a possible implementation strategy for future early intervention programs.

Methods

This retrospective cohort study used data from the California Cancer Registry (CCR) for patients diagnosed with stage I or II primary invasive HCC between January 1, 2005, and December 31, 2017. Our analysis was restricted to stage I or II disease to focus on HCC patients that would be amenable to curative-intent treatments. We defined curative-intent treatments as surgical resection, ablation, or transplantation; hereon, curative-intent treatments will be denotated as treatment. Locoregional therapies including transarterial chemoembolization (TACE), Y90, and radiation therapy (SBRT) are not captured as individualized codes as part of the CCR and therefore cannot be analyzed independently. Systemic therapy was not included as it is not the standard of care for early stage hepatocellular carcinoma. The primary outcome was receipt of treatment, and the secondary outcome was overall survival. All analyses were overseen by the institutional review board of University of California, Davis.

Hepatocellular carcinoma diagnoses were based on *International Classification of Diseases for Oncology* codes for site (C220) and histology (8170, 8172, 8173, 8174, and 8175). Clinical stage I or II patients were identified according to the American Joint Committee on Cancer (AJCC) (seventh edition) TNM staging criteria.[16] Patients with unknown or unspecified surgical coding (n=121), with missing race/ethnicity data (n=49), or with missing zip code data (n=17) were excluded. A total of 19,059 patients were included in the analysis.

Patient demographic, clinical and treatment characteristics were obtained from the CCR, including race/ethnicity, age, sex, marital status, date of diagnosis, tumor size, comorbidities, rural or urban residence, minimum distance to the nearest transplant center, type of health insurance, receipt of treatment at an NCI-designated cancer center; and neighborhood socioeconomic status (SES) quintile. Minimum distance to the nearest transplant center was calculated based on the geodetic distance in miles between two zip code locations. Private insurance included Health Maintenance Organization (HMO), Preferred Provider Organization (PPO), military funded, and Medicare with supplement. Public insurance included Medicare without supplemental insurance, Medicaid, Medicare/Medicaid dual eligible, county funded, and Indian/public health service.

Statistical analysis

Demographic and clinical variables were summarized for the study population using frequencies and percentages. The Kaplan-Meier method and log-rank test were used to determine overall survival differences by treatment and treatment type. Multivariable logistic regression was used to evaluate associations with receipt of treatment. Results are presented as adjusted odds ratios (OR) and 95% confidence intervals (CI). Additionally, multivariable Cox proportional hazards regression was used to evaluate associations with overall survival. Models included variables with a priori reasons for inclusion: stage at diagnosis, race/ethnicity, age, sex, marital status, Charlson comorbidity index, rural/urban residence, distance to nearest transplant center, health insurance, neighborhood SES quintile and treatment at an NCI-designated cancer center. Survival time was measured in years from the date of diagnosis to the date of death from any cause or the date of last follow-up

through October 2019. Results are presented as adjusted hazard ratios (HRs) and 95% confidence intervals (CI). Statistical analyses were performed with SAS software (version 9.4, SAS Institute, Cary, NC). All tests were two-sided and p-values < 0.05 were considered significant.

Results

Of 19,059 patients with early-stage HCC, only 36% (6,778) received treatment. The majority of patients presented with stage I disease (65%), were non-Hispanic White (39%), male (73%), and had more than one comorbidity (56%). Patients more commonly lived in urban areas (88%), with a mean distance of 37.2 miles (±42.9) from the nearest transplant center (Table 1). Nearly all patients had either private (51%) or public insurance (46%), with a very small proportion of uninsured patients (1.5%). Most patients did not receive care at an NCI-designated cancer center (64%). Of patients who received treatment, ablation (46%) and resection (36%) were more common than liver transplantation (18%). Univariate analyses by treatment status are shown in Table 1. Stage at diagnosis, tumor size, T category, race/ethnicity, mean age at diagnosis, marital status, comorbidities, residence type, distance from the nearest transplant center, insurance status, neighborhood SES quintile, and receipt of care at an NCI-designated center differed by treatment status ($p<0.05$).

Demographic characteristics associated with a decreased odds of receiving treatment were Hispanic ethnicity (OR 0.78, CI0.71–0.84; vs. non-Hispanic White), increasing age (OR 0.98, CI 0.98–0.98), male sex (OR 0.91, CI 0.85–0.98), being unmarried (OR 0.74, 0.69–0.79), rural residence (OR 0.88, CI 0.78–0.98), any type of non-private insurance, and lower neighborhood SES quintile (Table 2). Clinical characteristics associated with a decreased odds of receiving treatment included stage II disease (OR 0.73, CI 0.68–0.78), larger tumor size (OR 0.86, CI O.79–0.94 for 2–5 cm; OR 0.54, CI 0.49–0.60 for > 5cm), at least one comorbidity (OR 0.79, CI 0.74–0.85), or care at a non-NCI designated cancer center (OR 0.48, CI 0.45–0.51). In contrast, several characteristics were associated with greater odds of receiving treatment, specifically, Asian/Pacific Islander descent (OR 1.40, CI 1.28–1.53) and a residence located 20 to 50 miles from the nearest transplant center (OR 1.2, CI 1.10–1.31).

Lack of treatment was strongly associated with worse overall survival (multivariable-adjusted HR 2.85, CI 2.67–3.04). Treatment type was associated with survival (Figure 1). In multivariable survival models (Table 3), compared with resection, ablative treatments were associated with worse survival (HR 1.63, CI 1.51–1.76), while transplantation was associated with improved survival (HR 0.57, CI 0.51–0.65). Demographic characteristics associated with decreased survival were increasing age (HR 1.02, CI 1.02–1.02), male sex (HR 1.07, CI 1.03–1.11), being unmarried (HR 1.18, CI 1.14–1.23), a far travel distance to the nearest transplant center (>50 miles HR 1.11, CI 1.04–1.19), any non-private insurance type, and residing in the three lowest neighborhood SES quintiles. Clinical characteristics associated with decreased survival included stage II (vs. stage I) disease (HR 1.25, CI 1.20–1.30), larger tumor size (HR 1.33, CI 1.26–1.41 for 2–5 cm; HR 2.23, CI 2.10–2.38 for > 5cm), at least one comorbidity (HR 1.48, CI 1.42–1.53), and care at a non-NCI designated cancer center (1.33, CI 1.28–1.39). Hispanic ethnicity (vs. non-Hispanic White) was associated with improved overall survival (HR 0.94, CI 0.89–0.98).

Discussion

In this large, population-based study of early-stage HCC patients in California, we observed that 64% of patients did not receive treatment, with disparities in treatment observed by sociodemographic factors and type of treatment center. Hispanic patients were less likely and Asian/Pacific Islander patients were more likely to receive treatment than Non-Hispanic White patients. In addition, patients who did not receive treatment at an NCI-designated cancer center, lived in a lower SES neighborhood, and had any type of non-private insurance were less likely to receive treatment. Further, patients who lived farther from a transplant center, had any non-private insurance type, did not received treatment at an NCI-designated cancer center, and lived in a lower SES neighborhood experienced worse overall survival. Additionally, treatment was strongly associated with improved survival, with transplantation associated with superior overall survival compared with resection or ablation, as found previously.[17] Our findings suggest that early intervention programs should target travel barriers and referral and access to specialist care to help improve oncologic outcomes.

Our findings confirm the main hypothesis that travel distance to transplant center was associated with poorer survival in patients with early HCC in the state of California. This finding is consistent with prior studies in other phases of HCC care. In a recent population-based study, Goldberg et. Al[18] found that “remoteness” of specialty care was a predictor of decreased survival. Similarly, Moon et al[19] demonstrated that patients residing 50 miles or more from a transplant center had substantially decreased odds of visiting a transplant center for evaluation. Interestingly, other studies have shown some incongruent findings showing that hospital volume, rather than longer travel distance, appears to impact oncologic outcomes.[9,11] Interestingly, we found that receipt of treatment was associated with being farther away from a transplant center. This factor alone can therefore not explain the full picture. This is likely due to the complexity of care involved in HCC, such as diagnosis, surveillance, and other treatments not included in our analysis. For instance, several reports have shown rural residents were found to have lower rates of anti-viral treatment for hepatitis, decreased rates of surveillance, and higher stages of disease at diagnosis.[19–21] Therefore, the disparities noted in the current study of patients with early-stage HCC are likely multi-factorial and partially contributed to increased distance from specialty care. Furthermore, additional complexity is added when one considers that while distance from treatment centers is often measured in miles, this often understates travel difficulty.[22] Travel to urban centers within California from rural mountainous regions can be time consuming or challenging in certain months of the year. When designating critical access hospitals, Medicare recognizes facilities 35 miles or greater from the nearest other hospital as critical access; within mountainous regions, this distance is decreased to only 15 miles.[23]

Considering our second main finding that patients who received care at NCI-designated cancer centers were more likely to receive curative-intent treatment and experience improved survival, we must examine the unique characteristics of NCI-designated cancer centers in tandem with access to care issues. California is home to eight NCI-designated cancer centers, all of which are academic-affiliated, and either close to or are themselves, transplant facilities.[24] NCI-designated cancer centers bring together physicians skilled in complex clinical care and scientists working on novel treatments, such as

advanced procedural techniques and access to clinical trials opportunities. Furthermore, NCI-designated cancer centers often use a multidisciplinary team approach with discussion of patient cases at tumor boards with real-time peer review.[25] NCI-designated cancer centers have been shown to treat younger and healthier patients, but also perform more complex procedures with similar complication rates (except for surgical site infections).[26] These practices have been shown to contribute to improve survival.[27] Some studies suggest increased survival at NCI-designated cancer centers may result secondary to delayed dissemination of treatment advances in a rapidly advancing field.[28,29] Others have shown also that structural, organizational, or provider characteristics at centers with and without NCI-designation could explain observed associations in survival difference.[30] Nevertheless, efforts should be made to standardize care between all levels of oncologic institutes through the dissemination of best practices using common benchmarks and guidelines.

Lower neighborhood SES and lack of private insurance were independently associated with not receiving curative-intent treatment and worse overall survival. These results are consistent with findings in HCC and other advanced cancers where sociodemographic factors, such as lack of private insurance and lower SES, have been shown to influence survival.[3,8,18,19,31] Additionally, we demonstrated that unmarried patients were less likely to receive treatment and had worse overall survival, consistent with prior reports.[32,33] Treatment-based racial disparities reported in our findings were in congruence with national data in which Hispanic patients had significantly lower rates of curative resection or ablation. Similar patterns were also observed in association of SES, insurance, marital status, and survival in HCC patients.[3,34] Finally, we show that compared to Non-Hispanic Whites, Asian patients had the best survival. This could be explained due to the fact that they were likely to receive hepatectomy as described by others[6], underlying HCC etiology, access to screening programs[35], and have favorable SES factors.[36] Taken together, race/ethnicity, SES, and marital status are important demographic factors that contribute to one's social vulnerability, which has been consistently associated with poorer surgical treatment outcomes and worse survival.[37,38] In the context of HCC treatment, social vulnerability can impact the ease at which patients obtain prompt evaluation and care within certain hospital systems.

Limitations

There are several important limitations to our study inherent to the analysis of registry data. First, the accuracy of our data depends on the quality of information reported from medical facilities. Fortunately, the completeness of the CCR is estimated to be 95% or greater.[39] Most importantly, the CCR uses the AJCC TNM staging system which is limited in its clinical use. We understand that using the Barcelona Clinic Liver Cancer staging system is more comprehensive and rigorous to stage patients with HCC to guide clinical decision making. Additionally, other important variables, such as number of lesions (solitary vs multifocal disease), HCC etiology, degree of liver dysfunction (fibrosis, cirrhosis, portal hypertension), progression of disease or worsening of comorbidities are not collected in the CCR. These factors are important as they may have influenced therapy choices and could further contextualize our findings. Finally, the large number of patients not receiving treatment could be an overestimate, given the fact that locoregional therapies such as TACE,

Y90, and SBRT are not included in the registry. We also do not have information regarding the intent to treat for each patient (ie. bridging treatment to transplantation versus curative locoregional therapy). Despite these limitations, our study highlights an overall extremely low percentage of early-stage HCC patients receiving therapy and identifies type and distance to hospitality facility as two crucial factors to be considered in early intervention programs, specifically in California.

Conclusion

Our findings suggest that the majority of early-stage HCC patients in California do not receive therapy, which is associated with lower overall survival. We found that patients who received care at an NCI-designated cancer center and were in closer proximity to a transplant center had better overall survival even after controlling for known confounders. Considering that patients who received liver transplantation had substantially improved survival in our study, it is paramount that all eligible patients have equitable access to transplant specialist referral and resources to mitigate potential travel barriers to a transplant center. Improved partnership between community and NCI-designated cancer centers and regionalization of care has improved cancer care in other malignancies. Implementation of a rapid quality reporting system through the National Cancer Institute Community Care Centers Program showed significant improvements in several aspects of breast and colon cancer care.[40,41] Such quality improvement partnerships specific to prioritizing curative-intent treatments in early-stage HCC should be strongly considered to improve oncologic outcomes.

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Synopsis:

Our findings suggest that the majority of early-stage HCC patients in California do not receive therapy, which is associated with lower overall survival. We found that patients who received care at an NCI-designated cancer center and were in closer proximity to a transplant center had better overall survival even after controlling for known confounders.

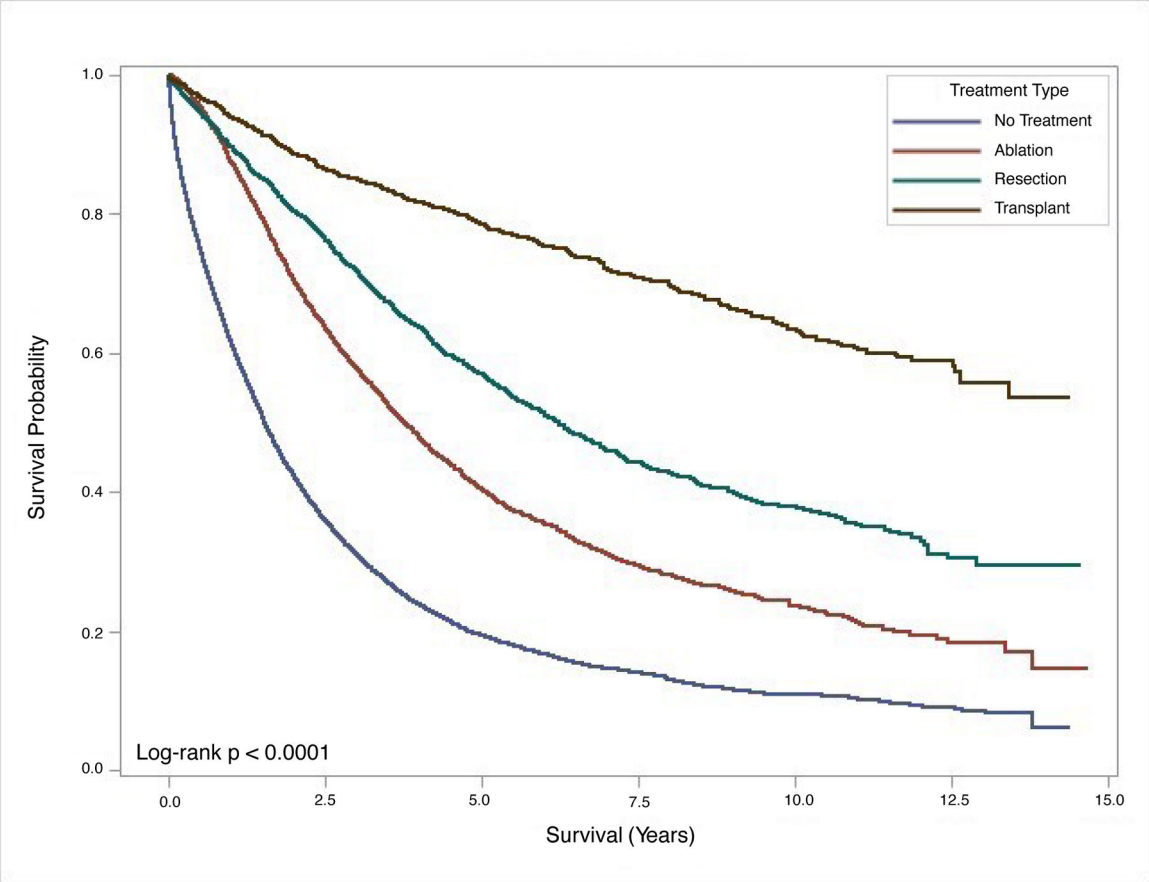

Figure 1:

Kaplan-Meier overall survival curves by treatment type among patients with early-stage HCC in California, 2005–2017.

Table 1.

Demographic and clinicopathologic characteristics by treatment in patients with early-stage HCC in California, 2005–2017.

Characteristics	Total N=19,059 n (col %)	Treatment N=6,778 n (col %)	No Treatment N=12,281 n (col %)	P value
Stage at diagnosis				
I	12,349 (64.8)	4,519 (66.7)	7,830 (63.8)	<0.001
II	6,710 (35.2)	2,259 (33.3)	4,451 (36.2)	
Tumor size				
≤ 2 cm	3,343 (17.5)	1,453 (21.4)	1,890 (15.4)	<0.001
2–5 cm	10,748 (56.4)	4,064 (60.0)	6,684 (54.4)	
> 5 cm	3,910 (20.5)	1,106 (16.3)	2,804 (22.8)	
Unknown	1,058 (5.6)	155 (2.3)	903 (7.4)	
T code				
T1	12,343 (64.7)	4,517 (66.7)	7,826 (63.7)	<0.001
T2	6,707 (35.2)	2,258 (33.3)	4,449 (36.2)	
Unknown	9 (0.1)	3 (0.0)	6 (0.1)	
Race/Ethnicity				
Non-Hispanic White	7,359 (38.6)	2,654 (39.2)	4,705 (38.3)	<0.001
Black	1,362 (7.1)	452 (6.7)	910 (7.4)	
Hispanic	5,730 (30.1)	1,650 (24.3)	4,080 (33.2)	
Asian/Pacific Islander	4,390 (23.0)	1,958 (28.9)	2,432 (19.8)	
Native American	218 (1.1)	64 (0.9)	154 (1.3)	
Age, years				
Mean (SD)	64.2 (±10.5)	62.8 (±9.9)	65.0 (±10.8)	<0.001
Range	20–101	20–95	20–101	
Sex				
Female	5,135 (26.9)	1,807 (26.7)	3,328 (27.1)	0.51
Male	13,924 (73.1)	4,971 (73.3)	8,953 (72.9)	
Marital status				
Married	10,148 (53.2)	4,079 (60.2)	6,069 (49.4)	<0.001
Not Married	8,342 (43.8)	2,521 (37.2)	5,821 (47.4)	
Unknown	569 (3.0)	178 (2.6)	391 (3.2)	
Charlson Comorbidity Index				
0,1	5,304 (27.8)	2,304 (34.0)	3,000 (24.4)	<0.001
>1	10,613 (55.7)	3,448 (50.9)	7,165 (58.3)	
Unknown	3,142 (16.5)	1,026 (15.1)	2,116 (17.2)	
Rural/Urban residence				
Rural	2,314 (12.1)	722 (10.7)	1,592 (13.0)	<0.001

Characteristics	Total N=19,059 n (col %)	Treatment N=6,778 n (col %)	No Treatment N=12,281 n (col %)	P value
Urban	16,745 (87.9)	6,056 (89.3)	10,689 (87.0)	
Distance to nearest transplant center[a], miles				
Mean (SD)	37.2 (±42.9)	35.5 (±40.9)	38.1 (±44.0)	<0.001
Median	19.4	19.6	19.3	
Range	0–272.3	0–267.0	0–272.3	
< 20 miles	9,666 (50.7)	3,396 (50.1)	6,270 (51.1)	
20 to 50 miles	4,698 (24.6)	1,845 (27.2)	2,853 (23.2)	
>50 miles	4,695 (24.6)	1,537 (22.7)	3,158 (25.7)	
Insurance[b]				
Private	9,750 (51.2)	3,963 (58.5)	5,787 (47.1)	<0.001
Public	8,754 (45.9)	2,680 (39.5)	6,074 (49.5)	
Uninsured	285 (1.5)	51 (0.8)	234 (1.9)	
Unknown	270 (1.4)	84 (1.2)	186 (1.5)	
Neighborhood SES quintile				
1 (lowest)	3,904 (20.5)	1,110 (16.4)	2,794 (22.8)	<0.001
2	4,283 (22.5)	1,408 (20.8)	2,875 (23.4)	
3	4,174 (21.9)	1,477 (21.8)	2,697 (22.0)	
4	3,742 (19.6)	1,488 (22.0)	2,254 (18.4)	
5 (highest)	2,956 (15.5)	1,295 (19.1)	1,661 (13.5)	
Treatment at NCI-designated cancer center				
Yes	6,882 (36.1)	3,249 (47.9)	3,633 (29.6)	<0.001
No	12,177 (63.9)	3,529 (52.1)	8,648 (70.4)	
Treatment type				
Resection	2,423 (12.7)	2,423 (12.7)	0	
Ablation	3,142 (16.5)	3,142 (16.5)	0	
Transplant	1,213 (6.4)	1,213 (6.4)	0	
No treatment	12,281 (64.4)	0	12,281 (64.4)	

Abbreviations: SD, standard deviation; SES, socioeconomic status; NCI, National Cancer Institute

[a]Based on distance between patient zip code and nearest transplant center zip code

[b]Private: includes HMO, PPO, military funded, and Medicare with supplement; Public: includes Medicaid, Medicare/Medicaid dual eligible, Medicare without supplement, county funded, Indian/public health service

Table 2.

Multivariate-adjusted odds ratios (OR) and associated 95% confidence intervals (CI) of associations with any curative-intent treatment among patients with early-stage HCC in California, 2005–2017.

Characteristics		
	OR (95% CI)	**P value**
Stage at diagnosis		
I	reference	
II	0.73 (0.68, 0.78)	< 0.001
Tumor size		
≤ 2 cm	reference	
2–5 cm	0.86 (0.79, 0.94)	< 0.001
> 5 cm	0.54 (0.49, 0.60)	< 0.001
Unknown	0.25 (0.21, 0.30)	< 0.001
Race/ethnicity		
Non-Hispanic White	reference	
Black	1.07 (0.94, 1.22)	0.32
Hispanic	0.78 (0.71, 0.84)	<0.001
Asian/Pacific Islander	1.40 (1.28, 1.53)	<0.001
Native American	0.87 (0.64, 1.18)	0.36
Age (1-year increments)	0.98 (0.98, 0.98)	<0.001
Sex		
Female	reference	
Male	0.91 (0.85, 0.98)	0.01
Marital status		
Married	reference	
Not Married	0.74 (0.69, 0.79)	<0.001
Unknown	0.85 (0.70, 1.03)	0.1
Charlson Comorbidity Index		
0,1, unknown	reference	
>1	0.79 (0.74, 0.85)	<0.001
Rural/Urban residence		
Rural	0.88 (0.78, 0.98)	0.03
Urban	reference	
Distance to nearest transplant center, miles[a]		
< 20 miles	reference	
20 to 50 miles	1.20 (1.10, 1.31)	<0.001
>50 miles	1.14 (1.00, 1.29)	0.06
Insurance[b]		
Private	reference	

Characteristics		
	OR (95% CI)	**P value**
Public	0.72 (0.67, 0.77)	<0.001
Uninsured	0.36 (0.26, 0.50)	<0.001
Unknown	0.71 (0.54, 0.94)	0.02
Neighborhood SES quintile		
1 (lowest)	0.65 (0.58, 0.73)	<0.001
2	0.73 (0.65, 0.81)	<0.001
3	0.79 (0.71, 0.88)	<0.001
4	0.90 (0.81, 1.00)	0.04
5 (highest)	reference	
Treatment at NCI designated cancer center		
Yes	reference	
No	0.48 (0.45, 0.51)	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval; SES, socioeconomic status; NCI, National Cancer Institute

[a]Based on distance between patient zip code and nearest transplant center zip code

[b]Private: includes HMO, PPO, military funded, and Medicare with supplement; Public: includes Medicaid, Medicare/Medicaid dual eligible, Medicare without supplement, county funded, Indian/public health service

Table 3.

Multivariate-adjusted hazard ratios (HR) and associated 95% confidence intervals (CI) of associations with overall survival among patients with early-stage HCC in California, 2005–2017.

Characteristics	Overall Survival	
	HR (95% CI)	P value
Stage at diagnosis		
I	reference	
II	1.25 (1.20, 1.30)	<0.001
Tumor size		
≤ 2 cm	reference	
2–5 cm	1.33 (1.26, 1.41)	<0.001
> 5 cm	2.23 (2.10, 2.38)	<0.001
Unknown	2.44 (2.24, 2.65)	<0.001
Race/ethnicity		
Non-Hispanic White	reference	
Black	1.03 (0.96, 1.11)	0.40
Hispanic	0.94 (0.89, 0.98)	0.004
Asian/Pacific Islander	0.75 (0.71, 0.79)	<0.001
Native American	1.01 (0.86, 1.18)	0.94
Age (1-year increments)	1.02 (1.02, 1.02)	<0.001
Sex		
Female	reference	
Male	1.07 (1.03, 1.11)	0.001
Marital status		
Married	reference	
Not Married	1.18 (1.14, 1.23)	<0.001
Unknown	1.15 (1.04, 1.28)	0.01
Charlson Comorbidity Index		
0,1, unknown	reference	
>1	1.48 (1.42, 1.53)	<0.001
Rural/Urban residence		
Rural	1.00 (0.94, 1.06)	0.96
Urban	reference	
Distance to nearest transplant center, miles[a]		
< 20 miles	reference	
20 to 50 miles	1.03 (0.98, 1.08)	0.20
>50 miles	1.11 (1.04, 1.19)	0.003
Insurance[b]		
Private	reference	

Characteristics	Overall Survival	
	HR (95% CI)	P value
Public	1.13 (1.09, 1.17)	<0.001
Uninsured	1.75 (1.52, 2.00)	<0.001
Unknown	1.39 (1.21, 1.59)	<0.001
Neighborhood SES quintile		
1 (lowest)	1.21 (1.13, 1.29)	<0.001
2	1.19 (1.12, 1.27)	<0.001
3	1.09 (1.02, 1.16)	0.01
4	1.05 (0.99, 1.12)	0.13
5 (highest)	reference	
Treatment at NCI designated cancer center		
Yes	reference	
No	1.33 (1.28, 1.39)	<0.001
Treatment type		
Resection	reference	
Ablation	1.63 (1.51, 1.76)	<0.001
Transplant	0.57 (0.51, 0.65)	<0.001
No treatment	2.85 (2.67, 3.04)	<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; SES, socioeconomic status; NCI, National Cancer Institute

[a]Based on distance between patient zip code and nearest transplant center zip code

[b]Private: includes HMO, PPO, military funded, and Medicare with supplement; Public: includes Medicaid, Medicare/Medicaid dual eligible, Medicare without supplement, county funded, Indian/public health service