Original Article

Racial disparities in treatment and survival of patients with hepatocellular carcinoma in the United States

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Background: While the incidence and mortality of hepatocellular carcinoma (HCC) continue to increase across the United States (US), disparities may exist relative to treatment modality and survival. The objective of the present study was to determine the factors associated with racial differences in survival among patients with HCC in the US.

Methods: The Surveillance, Epidemiology, and End Results (SEER) database was used to identify patients with HCC between 1998 and 2012 in the US. Multivariable logistic regression analysis was performed to examine associations between type of therapy and race, while a multivariable Cox proportional hazards model was built to determine the effect of race on survival.

Results: A total of 58,186 patients with HCC were identified. Over two-thirds of patients were white (n=39,223, 67.4%), while 18.3% were Asian (n=10,665), 13.1% black (n=7,620) and 1.2% native American (n=678). In comparison to other racial groups, Asian patients with HCC tended to be older [white *vs.* black *vs.* native American *vs.* Asian: median age: 63 years, interquartile range (IQR), 55-73 *vs.* 59 years, IQR, 53-66 *vs.* 59 years, IQR, 53-69 *vs.* 64 years, IQR, 55-73, P<0.001] and were diagnosed with larger tumors (white *vs.* black *vs.* native American *vs.* Asian: median tumor size: 4.8 cm, IQR, 3.0-8.0 *vs.* 5.1 cm, IQR, 3.1-8.7 *vs.* 4.8 cm, IQR, 3.0-7.3 *vs.* 5.5 cm, IQR, 3.1-9.0, P<0.001). Asian patients were also less likely to present with concomitant cirrhosis (white *vs.* black *vs.* native American *vs.* Asian: 81.8% *vs.* 77.7% *vs.* 83.2% *vs.* 69.1%, P<0.001) while elevated levels of alpha-fetoprotein more were often noted among black patients (white *vs.* black *vs.* native American *vs.* Asian: 25.5% *vs.* 14.9% *vs.* 22.2% *vs.* 21.8%, P<0.001). Compared to other racial groups, Asian patients were most likely to receive any form of treatment (white *vs.* black *vs.* native American *vs.* Asian: 29.2% *vs.* 25.2% *vs.* 27.6% *vs.* 34.4%, P<0.001). In particular, after controlling for potential confounders, Asian patients demonstrated the greatest odds of undergoing surgery (OR: 1.48, 95% CI, 1.13-1.95, P=0.01). The median overall survival (OS) was 11 months with the worst prognosis noted among black patients. After accounting for disease and patient factors, Asian patients demonstrated the lowest risk for death [hazard ratio (HR): 0.76, 95% CI, 0.66-0.87, P<0.001] while no differences were noted in the risk of death among other racial groups (all P>0.05).

Conclusions: Significant racial differences were noted in presentation, treatment and survival among patients with HCC. Further research is necessary to better understand socio-demographic and biological factors driving racial disparities in care. Future policies should aim to improve access to care among racial/ethnic minorities.

Keywords: Hepatocellular carcinoma (HCC); race; therapy; survival

Submitted Jul 12, 2015. Accepted for publication Aug 11, 2015.

doi: 10.3978/j.issn.2304-3881.2015.08.05

View this article at: http://dx.doi.org/10.3978/j.issn.2304-3881.2015.08.05

Introduction

Hepatocellular carcinoma (HCC) constitutes 4.6% of all new cancer cases and represents the fifth leading cause of cancer-related death worldwide (1-3). Although HCC is less common in the United States (US) compared with Africa and Eastern Asia, the incidence and mortality associated with HCC have been steadily increasing in the US over the past two decades (4-7). Furthermore, HCC is of interest in that it disproportionally affects all US racial/ethnic minority populations (8-10). In particular, the incidence of HCC is over two fold higher among Asian- and African-Americans compared with Caucasian patients in the US (8-10). Of note, recent studies have reported HCC-related mortality to have increased by 2.1%, 2.4% and 1.3% per year among white, black and Hispanic patients, respectively, between 2000 and 2010, but decreased by 1.6% per year among Asian patients (5).

Accounting for this disparity is likely multifaceted and may be due to social, biological and financial factors. For example, socioeconomic and insurance status may limit access to appropriate preventive and surveillance measures resulting in a higher incidence among older, minority and uninsured patients (8-10). Similarly, as complex surgical resection is the mainstay for treatment, patients may have to travel long distances to receive care at large, specialized centers. A recent study demonstrated that although only 40% of patients with HCC received surgical treatment, older patients as well as racial minorities had lower rates for surgery after controlling for disease and comorbid illnesses (9,11,12). Further, as demonstrated by Luo *et al*. cultural beliefs and attitudes as well as patient-physician communication can be critical to appropriate treatment decision-making among minority patients with cancer (11). In contrast, other reports have attributed this disparity to disease biology demonstrating that African Americans may present with more advanced, metastatic disease which may therefore be less amenable to cure (9). Although widely recognized and reported on for other cancers, data focusing on ethnicity-based clinical presentation, management, and survival among HCC patients are still limited. In addition, the reasons that drive racial differences in incidence and survival among these patients remain poorly understood. Given this, the present study aimed to examine racial differences in treatment modality and survival among patients presenting with HCC in the US.

Methods

Data sources and study population

Patients presenting with HCC were identified using the Surveillance Epidemiology, and End Results (SEER) database from 1998 to 2012 (13). Maintained by the National Cancer Institute, the SEER registry database collects patient and disease specific data from local and regional cancer registries and is a representative sample of 28% of the US population. Standard patient demographic and clinicopathologic data including gender, age at diagnosis, year of diagnosis, tumor size, stage at diagnosis, alpha fetoprotein (AFP) levels, presence of cirrhosis, and tumor grade of differentiation were collected.

Patients with HCC were identified using International Classification of Diseases for Oncology, Third Edition (ICD-O-3) topography and morphology codes. Specifically "primary site" code "C220" and "histologic type" codes "8170," "8172," "8173," "8174," and "8175" were used to select for patients. A confirmed diagnosis of HCC was defined as either a positive microscopic result, laboratory test/marker, direct visualization, or positive radiology and imaging. Patients with histology codes other than those representing HCC and patients with HCC diagnosed upon autopsy were excluded from the analysis. Similarly, records with missing information for age, and race as well as patients younger than 18 years were excluded. Further, due to marked differences in epidemiology and prognosis, patients presenting with fibrolamellar carcinoma was also excluded from the study cohort (14,15).

Patient race was categorized as white, black, Asian (Asian/Pacific Islander), and native American (American Indian/Alaska native) based on SEER coding scheme (13). Type of treatment was determined using SEER site-specific surgery of primary site codes and radiation therapy codes. Surgical management was defined as either a liver resection and/or a liver transplant while ablation was defined as heat-radio-frequency ablation, photodynamic therapy, electrocautery, fulguration, cryosurgery, laser, or alcohol and acetic acid ablation and considered as non-surgical treatment. Patients were categorized into treatment groups based on the treatment received for primary disease. In the instance where a patient received multiple types of treatments for the same disease episode, they were categorized based on highest level of treatment. For example, if a patient underwent both radiation and surgery, they were categorized as having undergone surgery for their primary disease. Stage at diagnosis was defined as either localized, regional disease, distant disease, or unstaged. Tumor grade was classified using SEER grading and differentiation codes whereby grade I represented well-differentiated disease, grade II; moderately differentiated, grade III; poor differentiated and grade IV

representing undifferentiated disease. For ease of analysis, grade was categorized as a binary variable combing grades I and II into a single category and grades III and IV into another. Cirrhosis was defined using the SEER site-specific fibrosis score, classifying patients presenting with a fibrosis score of ≥5 as cirrhotic. Vital status was recorded for all cases, and the date of latest follow-up was December 31, 2012.

Statistical analysis

Descriptive statistics were reported as medians with interquartile range (IQR) for continuous variables and as whole numbers and percentages for categorical variables. Descriptive statistics for discrete variables were compared using the Chi square and Fisher's exact test, where appropriate. The Kruskal-Wallis test was used to compare continuous variables. Multivariable logistic regression analysis was performed to identify factors determining treatment modality for HCC (surgical *vs.* non-surgical therapy). The Kaplan-Meier method was used to assess stage-adjusted and treatment-adjusted survival. A multivariable Cox proportional hazards models was built to determine factors predictive of survival. All variables of clinical importance were included in multivariable analysis. Since AFP and cirrhosis are important clinical factors for treatment and survival of HCC, only patients with information pertaining to AFP and severity of cirrhosis were included in multivariable analysis (patients diagnosed after 2004). The prognostic power of covariates was expressed as HRs with 95% confidence intervals. Statistical significance was defined as P<0.05 (two-sided). All analyses were performed using STATA version 12.0 (StataCorp LP, College Station, TX, USA).

Results

Racial disparities in demographic and tumor features

A total of 58,186 patients with HCC were identified and met inclusion criteria. The median age of the cohort was 62 years (IQR, 55-73 years) with a majority of patients being male (n=44,339, 76.2%). Over two-thirds of patients were white (n=39,223, 67.4%) while 13.1% (n=7,620) of the cohort were black, 1.2% (n=678) native American and 18.3% (n=10,665) Asian. The median tumor size was 5.0 cm (IQR, 3.0-8.0) with approximately half of all patients presenting with localized disease (n=27,207, 46.8%) and 24.8% (n=5,600) of patients presenting with high grade (grade III or IV) lesions. Data pertaining to serum AFP and cirrhosis were available for 32,109 and 10,263 patients respectively. Among these patients, 23.3% (n=7,484) presented with elevated AFP levels at diagnosis while a majority of patients had concomitant cirrhosis (n=8,117, 79.1%) (*Table 1*).

Marked differences were noted in baseline demographic and disease characteristics by race (*Table 1*). For example, white and Asian patients were older compared with black and native American patients (white *vs.* black *vs.* native American *vs.* Asian: median age: 63 years, IQR, 55-73 *vs.* 59 years, IQR, 53-66 *vs.* 59 years, IQR, 53-69 *vs.* 64 years, IQR, 55-73, all P<0.001). Similarly, Asian and Native American patients were more likely to be female *vs.* white and black patients (white *vs.* black *vs.* native American *vs.* Asian: 22.8% *vs.* 22.8% *vs.* 28.6% *vs.* 27.8%, all P<0.001). On average, Asian patients presented with larger tumors compared with other racial groups (white *vs.* black *vs.* native American *vs.* Asian: median tumor size: 4.8 cm, IQR, 3.0-8.0 *vs.* 5.1 cm, IQR, 3.1-8.7 cm *vs.* 4.8 cm, IQR, 3.0-7.3, *vs.* 5.5 cm, IQR, 3.1-9.0, all P<0.05) and were more likely to present with localized disease (white *vs.* black *vs.* native American *vs.* Asian: 47.2% *vs.* 43.2% *vs.* 45.0% *vs.* 47.8%, all P<0.05). Compared with other racial groups, Asian patients were proportionally less likely to present with cirrhosis at diagnosis (white *vs.* black *vs.* native American *vs.* Asian: 81.8% *vs.* 77.7% *vs.* 83.2% *vs.* 69.1%, all P<0.05). While an elevated AFP was detected in over a fifth of patients, black patients were the least likely to present with an elevated AFP at diagnosis (white *vs.* black *vs.* native American *vs.* Asian: 25.5% *vs.* 14.9% *vs.* 22.2% *vs.* 21.8%, all P<0.001).

Racial disparities in treatment

Among all patients, less than 30% of patients received any type of treatment for HCC (n=12,789, 29.5%), with Asian patients more likely to receive treatment for HCC compared with other racial groups (white *vs.* black *vs.* native American *vs.* Asian: 29.2% *vs.* 25.2% *vs.* 27.6% *vs.* 34.4%, all P<0.001). In addition, differences in the type of treatment were also noted by race among patients that received any form of treatment for HCC. For example, Asian patients were proportionally more likely to be treated surgically either with resection or a liver transplant compared with other racial groups (white *vs.* black *vs.* Native American *vs.* Asian: 14.3% *vs.* 11.8% *vs.* 10.1% *vs.* 19.4, all P<0.001, *Table 1*). Similar patterns in treatment

Table 1 Demographic and tumor-related features compared by race among patients with hepatocellular carcinoma between 1998 and 2012 in SEER registries

Variables	Total (n=58,186)	White (n=39,233)	Black (n=7,620)	Native American (n=678)	Asian (n=10,655)	P
Time of diagnosis						<0.001
1998-2003	14,902 (25.6)	9,761 (24.9)	1,733 (22.8)	146 (21.5)	3,262 (30.6)	
2004-2008	21,077 (36.2)	14,168 (36.1)	2,761 (36.2)	252 (37.2)	3,896 (36.6)	
2009-2012	22,207 (38.2)	15,304 (39.0)	3,126 (41.0)	280 (41.3)	3,497 (32.8)	
Age, years, median [IQR]	62 [55-73]	63 [55-73]	59 [53-66]	59 [53-69]	64 [55-73]	<0.001
Age (year)						<0.001
18-39	963 (1.7)	414 (1.1)	177 (2.3)	9 (1.3)	363 (3.4)	
40-59	22,705 (39.0)	15,029 (38.3)	3,749 (49.2)	333 (49.1)	3,594 (33.7)	
60-69	15,828 (27.2)	10,462 (26.7)	2,287 (30.0)	179 (26.4)	2,900 (27.2)	
≥70	18,690 (32.1)	13,328 (34.0)	1,407 (18.5)	157 (23.2)	3,798 (35.7)	
Gender						<0.001
Male	44,339 (76.2)	30,280 (77.2)	5,880 (77.2)	484 (71.4)	7,695 (72.2)	
Female	13,847 (23.8)	8,953 (22.8)	1,740 (22.8)	194 (28.6)	2,960 (27.8)	
Tumor grade (n=22,589)						<0.001
I	7,683 (34.0)	5,430 (35.6)	974 (33.1)	71 (31.0)	1,208 (29.0)	
II	9,306 (41.2)	6,190 (40.6)	1,233 (41.9)	95 (41.5)	1,788 (42.9)	
III	5,079 (22.5)	3,277 (21.5)	676 (22.9)	58 (25.3)	1,068 (25.7)	
IV	521 (2.3)	353 (2.3)	63 (2.1)	5 (2.2)	100 (2.4)	
Tumor size, cm, median (IQR)	5.0 (3.0-8.0)	4.8 (3.0-8.0)	5.1 (3.1-8.7)	4.8 (3.0-7.3)	5.5 (3.1-9.0)	<0.001
Stage at diagnosis						<0.001
Localized	27,207 (46.8)	18,513 (47.2)	3,293 (43.2)	305 (45.0)	5,096 (47.8)	
Regional spread	15,188 (26.1)	10,018 (25.5)	2,101 (27.6)	186 (27.4)	2,883 (27.1)	
Distant spread	10,517 (18.1)	6,913 (17.6)	1,590 (20.9)	124 (18.3)	1,890 (17.7)	
Unstaged	5,274 (9.0)	3,789 (9.7)	636 (8.3)	63 (9.3)	786 (7.4)	
AFP (n=32,109)						<0.001
Positive	7,484 (23.3)	5,474 (25.5)	671 (14.9)	88 (22.2)	1,251 (21.8)	
Negative	24,533 (76.4)	15,929 (74.2)	3,812 (84.9)	306 (77.3)	4,486 (78.1)	
Borderline	92 (0.3)	71 (0.3)	10 (0.2)	2 (0.5)	9 (0.1)	
Cirrhosis (n=10,263)						<0.001
F0	2,146 (20.9)	1,282 (18.2)	274 (22.3)	27 (16.8)	563 (30.9)	
F1	8,117 (79.1)	5,770 (81.8)	953 (77.7)	134 (83.2)	1,260 (69.1)	
Type of therapy						<0.001
None	40,813 (70.1)	27,566 (70.3)	5,656 (74.2)	504 (74.3)	7,087 (66.5)	
Radiation only	2,561 (4.4)	1,816 (4.6)	386 (5.1)	32 (4.7)	327 (3.1)	
Ablation	5,365 (9.2)	3,616 (9.2)	566 (7.4)	67 (9.9)	1,116 (10.5)	
Resection	5,231 (9.0)	3,021 (7.7)	623 (8.2)	46 (6.8)	1,541 (14.4)	
Transplant	3,186 (5.5)	2,481 (6.3)	257 (3.4)	24 (3.5)	424 (4.0)	
Unknown	1,030 (1.8)	733 (1.9)	132 (1.7)	5 (0.8)	160 (1.5)	

SEER, Surveillance, Epidemiology, and End Results Program; IQR, interquartile range; tumor grade I, well differentiated; tumor II, moderately differentiated; tumor III, poorly differentiated; tumor IV, undifferentiated; AFP, alpha fetal protein; F0, fibrosis score 0-4, none to moderate fibrosis; F1, fibrosis score 5-6, severe fibrosis or cirrhosis.

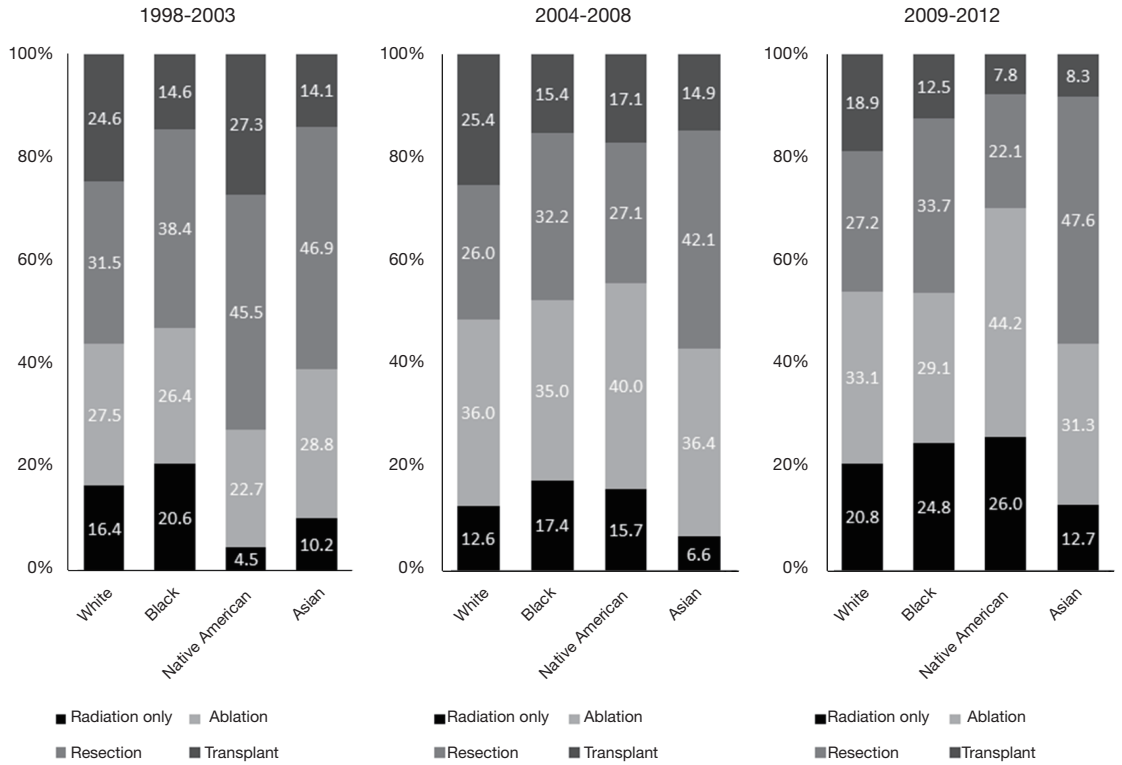

Figure 1 Proportion of different treatments for hepatocellular carcinoma stratified by race across different time periods examined.

were also noted throughout the time period of the study among the different racial groups (*Figure 1*). Of note, among patients that received any form of treatment, white patients were the racial group most likely to receive a liver transplant compared with other racial groups. This pattern was consistent throughout the study period. The proportion of patients that underwent ablation of a lesion increased throughout the study time period with a similar trend observed among all racial groups. Specifically among patients that received any form of treatment 18.0% (n=43) patients received an ablation for their lesion in 1998 compared to 36.2% (n=398) in 2004 and 33.4% (n=563) in 2012, with Native American patients proportionally more likely to be managed via ablation compared to all other racial groups (*Figure 1*).

To assess the factors associated with receiving surgical treatment (liver resection and/or transplant) for HCC, multivariable analysis was performed controlling for patient demographics and disease characteristics (*Table 2*). In particular, increasing age was associated with decreased odds of undergoing surgery (60-69 years: OR: 0.71, 95% CI, 0.56-0.89, P=0.004; ≥70 years: OR: 0.42, 95% CI, 0.31-0.56, P<0.001) while female patients demonstrated greater odds to undergo surgery compared with male patients (OR: 1.43, 95% CI, 1.10-1.87, P=0.01). Interestingly, while white, black and Native American patients were just as likely to undergo surgery, Asian patients demonstrated a 48% greater odds of undergoing surgery (OR: 1.48, 95% CI, 1.13-1.95, P=0.01). Similarly, patients with higher tumor grade demonstrated greater odds of undergoing surgery (grade III/IV: OR: 1.71, 95% CI, 1.26-2.33) while patients with metastatic disease (regional metastasis: OR: 0.74, 95% CI 0.58-0.96, P=0.02; distant metastasis: OR: 0.21, 95% CI, 0.11-0.39, P<0.001) as well as patients with elevated AFP (OR: 0.64, 95% CI, 0.51-0.80, P<0.001) or cirrhosis at diagnosis (OR: 0.60, 95% CI, 0.47-0.77, P<0.001) demonstrated decreased odds of undergoing surgery (*Table 2*).

Racial disparities in overall survival (OS)

Median OS for the entire cohort was 11 months while 1-, 3-, and 5-year survival were 47.8%, 25.5%, and 18.1%, respectively. Racial differences were noted in OS. Asian patients demonstrated the highest OS of 15 months compared with white, black and native American patients who had an OS of 11 months, 9 months and 12 months,

Table 2 Results from the multivariable logistic regression examining the factors associated with receipt of surgical therapy among patients with hepatocellular carcinoma

Predict variables	Adjusted OR	95% CI	P
Race			
White	1	–	Reference
Black	1.06	0.76-1.48	0.73
Native American	1.33	0.55-3.16	0.53
Asian	1.48	1.13-1.95	0.01
Age (year)			
18-39	7.6	1.02-56.69	0.05
40-59	1	–	Reference
60-69	0.71	0.56-0.89	0.004
≥70	0.42	0.31-0.56	<0.001
Gender			
Male	1	–	Reference
Female	1.43	1.10-1.87	0.01
Tumor size (cm)	1	1.00-1.01	0.01
Tumor grade			
I/II	1	–	Reference
III/IV	1.71	1.26-2.33	0.001
Stage at diagnosis			
Localized	1	–	Reference
Regional spread	0.74	0.58-0.96	0.02
Distant spread	0.21	0.11-0.39	<0.001
Unstaged	NA	NA	NA
AFP			
Negative	1	–	Reference
Positive	0.64	0.51-0.80	<0.001
Cirrhosis			
F0	1	–	Reference
F1	0.6	0.47-0.77	<0.001

OR, odds ratio; CI, confidence interval; tumor grade I, well differentiated; tumor II, moderately differentiated; tumor III, poorly differentiated; tumor IV, undifferentiated; NA, not applicable; AFP, alpha fetal protein; F0, fibrosis score 0-4, none to moderate fibrosis; F1, fibrosis score 5-6, severe fibrosis or cirrhosis.

respectively (all P<0.05). Similarly, 5-year survival was highest among Asian patients compared with other racial groups (white *vs*. black *vs*. native American *vs*. Asian: 17.5% *vs*. 12.4% *vs*. 17.7% *vs*. 23.8%, all P<0.001). These racial differences in survival were also noted after stratifying by disease stage (*Figure 2A,B*). Specifically, among patients with localized disease, 1-, 3- and 5-year OS was highest among Asian patients (white: 62.8%, 37.1%, 27.2% *vs*. black: 60.5%, 31.8%, 21.2% *vs*. native American: 63.5%, 37.8%, 27.2% *vs*. Asian: 71.4%, 47.5%, 36.1%, all P<0.05). In contrast, patients with metastatic disease, 1-, 3-, and 5-year OS was lowest among black patients (white: 30.5%, 11.6%, 7.5% *vs*. black: 25.7%, 8.7%, 4.5% *vs*. native American: 30.6%, 13.7%, 8.6% *vs*. Asian: 34.0%, 15.7%, 10.8%, all P<0.05).

A similar trend in survival was noted among racial groups when stratified by treatment. Among patients who underwent surgery, black patients had the worst prognosis compared with other races, while a similar survival was noted among white and Asian patients (1-, 3- and 5- years OS: white 84.3%, 66.0%, 54.7% *vs*. black: 81.3%, 55.3%, 40.9% *vs*. native American: 76.8%, 65.3%, 57.8% *vs*. Asian: 82.8%, 64.6%, 53.5%, P<0.001, *Figure 2C*). For patients who were managed non-surgically, Asian patients demonstrated the best prognosis while black patients demonstrated the lowest survival. Specifically, the 1-, 3-, and 5-year OS of Asian patients who underwent non-surgical therapy were 72.2%, 44.3%, and 31.3%, *vs*. 61.8%, 29.6%, and 17.8% among white patients (P<0.001), and 58.0%, 26.5%, and 14.5% among black patients (P<0.001, *Figure 2D*).

On multivariable analysis after adjusting for patient and disease characteristics, Asian patients demonstrated the lowest risk of death compared with white patients (HR: 0.76, 95% CI, 0.66-0.87, P<0.001). In addition, no differences in survival were noted among white, black and native American patients (all P>0.05, *Table 3*). Other patient and disease characteristics associated with a poor prognosis included age ≥70 years (HR: 1.21, 95% CI, 1.06-1.38, P=0.01), tumor size (HR: 1.01, 95% CI, 1.01-1.01, P<0.001), a higher tumor grade (grade III/IV: HR: 1.48, 95% CI, 1.30-1.69, P<0.001), metastatic disease (regional metastasis: HR: 1.42, 95% CI, 1.26-1.61, P<0.001; distant metastasis: HR: 2.07, 95% CI, 1.70-2.53, P<0.001), elevated AFP levels (HR: 1.36, 95% CI, 1.20-1.54, P<0.001) and cirrhosis at presentation (HR: 1.39, 95% CI, 1.20-1.58, P<0.001). Furthermore, compared to patients that did not receive any treatment, patients that received a liver transplantation demonstrated the lowest risk of death (HR: 0.14, 95% CI, 0.11-0.17, P<0.001) followed by patients that underwent a surgical resection (HR: 0.35, 95% CI, 0.30-0.41, P<0.01) or ablation (HR: 0.52, 95% CI, 0.44-0.61, P<0.001). Of note, radiation

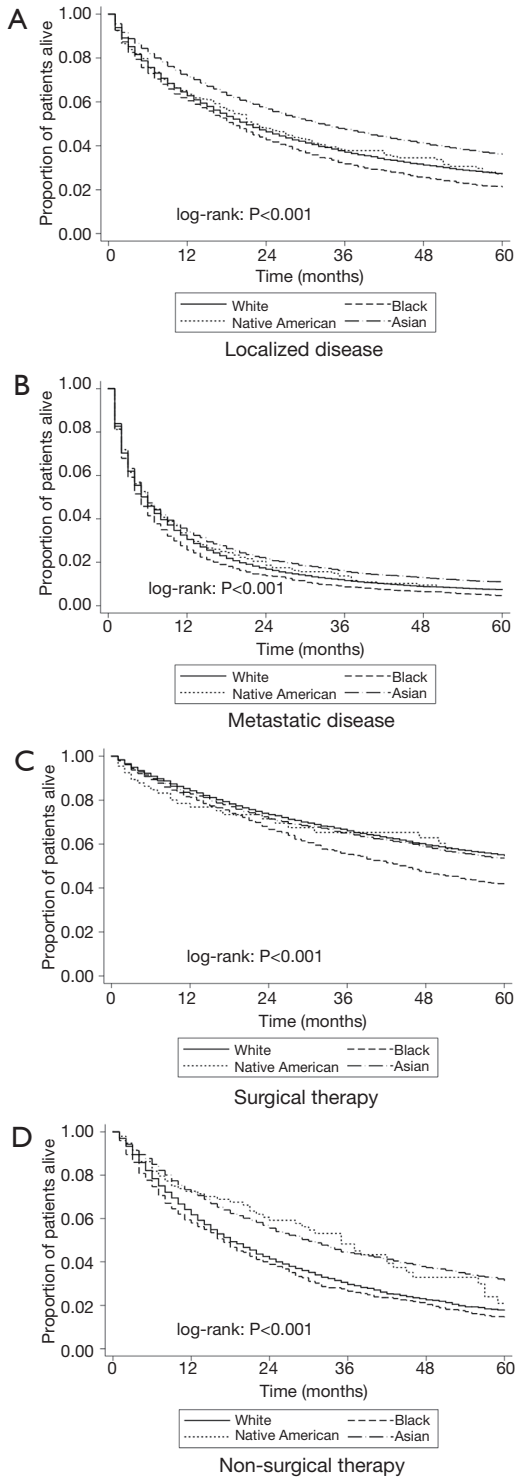

Figure 2 Kaplan-Meier curves for patients with hepatocellular carcinoma by race, stratified by stage of disease and type of treatment. (A) Localized disease; (B) metastatic disease; (C) surgical therapy; (D) non-surgical therapy.

Table 3 Results from the multivariable Cox regression examining factors associated with risk of death in patients with hepatocellular carcinoma

Predict variables	Adjusted HR	95% CI	P value
Race			
White	1	–	Reference
Black	1.07	0.91-1.26	0.38
Native American	0.81	0.52-1.26	0.35
Asian	0.76	0.66-0.87	<0.001
Age (year)			
<40	1.12	0.76-1.66	0.57
40-59	1	–	Reference
60-69	0.98	0.86-1.11	0.74
≥70	1.21	1.06-1.38	0.01
Gender			
Male	1	–	Reference
Female	0.99	0.87-1.12	0.88
Tumor size (cm)	1.01	1.01-1.01	<0.001
Tumor grade			
I/II	1	–	Reference
III/IV	1.48	1.30-1.69	<0.001
Stage at diagnosis			
Localized	1	–	Reference
Regional spread	1.42	1.26-1.61	<0.001
Distant spread	2.07	1.70-2.53	<0.001
Unstaged	1.16	0.60-2.27	0.66
AFP			
Negative	1	–	Reference
Positive	1.36	1.20-1.54	<0.001
Cirrhosis			
F0	1	–	Reference
F1	1.39	1.20-1.58	<0.001
Type of therapy			
None	1	–	Reference
Radiation only	0.81	0.60-1.08	0.15
Ablation	0.52	0.44-0.61	<0.001
Resection	0.35	0.30-0.41	<0.001
Transplant	0.14	0.11-0.17	<0.001

HR, hazard ratio; CI, confidence interval; tumor grade I, well differentiated; tumor II, moderately differentiated; tumor III, poorly differentiated; tumor IV, undifferentiated; AFP, alpha fetal protein; F0, fibrosis score 0-4, none to moderate fibrosis; F1, fibrosis score 5-6, severe fibrosis or cirrhosis.

alone did not decrease the risk of death among patients with HCC (HR: 0.81, 95% CI, 0.60-1.08, P=0.15, *Table 3*).

Discussion

HCC represents the third leading cause of cancer-related death worldwide (1,2). Although HCC is less frequently encountered in the US compared with Africa and Eastern Asia, recent years have seen a steady increase in the incidence and mortality of HCC in the US (4-6). Of note, recent studies have suggested that racial differences exist among patients with HCC with regard to incidence and mortality (7,8,10,16). Using a nationally representative cohort of patients with HCC, the present study characterized racial differences in survival and treatment choices among patients. To our knowledge, this is the first study to report racial disparities among patients undergoing medical or surgical treatment for HCC in the US over a span of over 20 years. In particular, we noted significant differences in presentation by race with black patients being more likely to present with metastatic disease, while Asian patients were the least likely to present with concomitant liver cirrhosis. After accounting for patient and disease characteristics, Asian patients were most likely to undergo a liver resection, with liver transplantation being more common among white patients. Furthermore, Asian patients demonstrated a 24% lower risk of mortality compared with white patients.

While racial disparities have been well-documented for multiple cancers, less is known regarding racial disparities for HCC. In the current study of over 58,000 patients, we noted racial differences not only in the treatment of HCC but also significant differences in disease presentation by race. These data suggest that etiological factors as well as socio-demographic factors may play important roles in explaining observed disparities. For example, previous reports have demonstrated that Asian patients tend to present with HCC that develops in a non-cirrhotic liver due to chronic hepatitis B virus infection and therefore may be more amenable to surgery (8,17,18). Supporting this notion, the current study noted that Asian patients were the racial group least likely to present with underlying cirrhosis. In addition, Asian patients also had a 48% greater odds of undergoing surgical resection for HCC compared with white patients. In contrast, the current study noted that black patients were proportionally more likely to present at a later stage/with metastatic disease. While recent reports suggest genetic variations in tumor biology and pathogenesis among patients, differences noted in our study also serve to highlight disparities in access to adequate screening and preventive measures. In their recent report, Davila *et al*. reported significantly lower rates of screening and surveillance for HCC among black and Hispanic patients while Asian patients, patients of a higher median household income and patients with a higher level of education were almost two-fold more likely to receive HCC surveillance (19). These data are consistent with findings from the current study that noted a large variation in the stage of disease among patients from different racial groups. Taken together, the data suggest that while potentially efficacious interventions in the form early detection via the use of surveillance ultrasounds and targeted, more frequent screening programs for HCC among high-risk groups are available, access to such parameters are limited and can vary by racial/ethnic groups. In turn, these socio-demographic inequalities may result in disparities in treatment and subsequent survival.

In addition to variations in screening, differences in treatment choices may also be affected by patient preferences, socio-demographic differences and access to care (8,10). The decision-making process for treatment among HCC patients is complicated, especially given the advent of novel therapies and the increasing use of a multidisciplinary approach (20). With patients increasingly involved in the selection of their treatment, cultural attitudes and communication between patient and provider can significantly affect choice of treatment (9,11). For example, Lin *et al*. reported higher levels of medical mistrust and fatalism among certain minority patients undergoing cancer surgery (21). Coupled together, medical mistrust and fatalism have been associated with decreased follow-ups, lower adherence to treatment plans as well as higher rates of refusal for potentially curative surgery. Mathur *et al*. noted that even among patients presenting with early stage HCC, only 40% of patients received surgery with markedly lower rates among minority, uninsured and elderly patients (8). Similarly Zak and colleagues reported that minority serving hospitals were less likely to offer surgical treatment after accounting for disease severity (9). In the current study, we similarly noted that differences in receipt of treatment among different patient cohorts. For example, Asian patients were proportionally more likely to be treated surgically either with resection or a liver transplant compared with other racial groups (white *vs*. black *vs*. native American *vs*. Asian: 14.3% *vs*. 11.8% *vs*. 10.1% *vs*. 19.4, P<0.001) (*Figure 1*). In turn, perhaps not surprisingly, these differences in disease presentation and receipt of treatment translated into disparate race based survival outcomes. Specifically, Asian

patients had an overall better survival compared with other racial groups even after controlling for available factors in the dataset. In contrast, black patients had the worst survival. Moving forward, policies will need to be developed that specifically target racial disparities such as implementing culturally sensitive screening and preventive programs, as well as increasing awareness and education regarding disparities in HCC outcomes among health care providers.

The current study had several limitations. There may have been some discordance in the reporting of race between self-reported and registry records, which may have possibly impacted the results (12). However, any reporting bias would likely be random and not affect the main findings of the study. Further, the lack of granular information pertaining to tumor specific data including the Barcelona clinic liver cancer (BCLC) staging system and other clinically relevant risk factors such as preexisting hepatitis infections limited our ability to explain differences in disease presentation. Similarly, a lack of data pertaining to the use of trans arterial chemo-embolization, systemic chemotherapy or laparoscopic ablation in the SEER-dataset may have led to an underestimation of certain treatment received. Finally, details pertaining to socioeconomic and insurance status, which may play an important role in driving differences in treatment and survival, were not available in the SEER-database and therefore could not be accounted for.

Conclusions

In conclusion, treatment and mortality for HCC in the US vary substantially by race. After adjusting for several disease factors, Asian patients were more likely to undergo potentially curative therapy such as resection and transplantation and, in turn, Asian patients with HCC had the best OS compared with other racial groups. In contrast, black patients were less likely to receive treatment and demonstrated a worse prognosis compared with other racial groups. Future policies should focus of improving access to care/treatment among minority groups, which is a prerequisite to improving outcomes for all racial groups. In addition, future studies should continue to characterize socioeconomic factors that may determine choice of treatment modality, as well as genetic factors that might impact survival of patients with HCC.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The IRB waiver for this study was obtained.

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Cite this article as: Xu L, Kim Y, Spolverato G, Gani F, Pawlik TM. Racial disparities in treatment and survival of patients with hepatocellular carcinoma in the United States. Hepatobiliary Surg Nutr 2016;5(1):43-52. doi: 10.3978/j.issn.2304-3881.2015.08.05

