Clinical Features Associated with Survival Outcome in African-American Patients with Hepatocellular Carcinoma

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BACKGROUND: **African-Americans (AA) have a higher incidence of hepatocellular carcinoma (HCC) and lower survival. We characterized survival rates and clinical features associated with survival in AA vs. Caucasians with HCC over the past two decades.**

METHODS: **HCC patients from three US medical centers were matched by year of diagnosis (1991–2016): AA (n = 578)/Caucasian (n = 578) and placed in one of two groups—HCC diagnosed prior to 2010 or 2010 and after. Data were obtained from chart review and the National Death Index. Multivariate and survival analysis controlling for key predictors were conducted.**

RESULTS: **Prior to 2010, there was no difference in survival between Caucasians and AA (p = 0.61). After 2010, AA patients had poorer survival compared to Caucasians (35% vs. 44%, respectively, p = 0.044). Over time, survival improved for Caucasians (32% before 2010 vs. 44% after 2010, p = 0.003), but not AA (36% vs. 35%, p = 0.50). AA on presentation (in the after 2010 cohort) were more likely to have BCLC (Barcelona Clinic Liver Cancer) stage C (24% vs. 15%, p = 0.010) and less likely to receive treatment (85% vs. 93%, p = 0.002) compared to matched Caucasians. BCLC beyond stage A (aHR: 1.75, 95% CI: 1.26–2.43, p = 0.001) and child's class C (aHR 2.05, 95% CI: 1.23–3.41, p = 0.006) were the strongest predictors of mortality, while race was not.**

CONCLUSIONS: **African-Americans presented with more advanced HCC and had poorer survival compared to Caucasians after 2010. Tumor stage was an independent predictor of mortality, but ethnicity was not. Further efforts are needed to improve early HCC diagnosis for AA.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/A29

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INTRODUCTION

Worldwide, more than half a million cases of hepatocellular carcinoma (HCC) are diagnosed annually (1), making HCC the third most common cause of cancer-related deaths (2). In the United States (US), liver cancer, particularly HCC, is one of the leading causes of cancer-related deaths (3), which may continue to be a leading cause as the overall incidence of HCC continues to increase (2).

Though most cases of HCC are caused by chronic viral infections with hepatitis B or C virus (4), the distribution of HCC etiologies varies widely depending on geographic location and ethnicity. For example, chronic hepatitis B is the leading cause of HCC in certain parts of Asia and Africa, while chronic hepatitis C is more common in Japan, Italy, and the US (5,6).

In the US, HCC incidence and mortality are higher in African-Americans compared to Caucasians (1,2,7–9). Several studies have shown that African-American ethnicity to be an independent risk factor for HCC mortality (2,7,9). However, many of these studies lack information on liver disease etiology, severity of the underlying liver disease (degree of hepatic dysfunction and/or cirrhosis status), and/or accurate HCC staging. As a result, it is difficult to discern why this racial disparity exists. Our aim was to examine the differences in HCC etiologies, treatment, and survival between African-American and Caucasian patients and to examine predictors of survival, including ethnicity, etiology of underlying liver disease, HCC stage, year of HCC diagnosis, and treatment modality.

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METHODS

Study design and patient population

We performed a cohort study of HCC cases enrolled at Stanford University Medical Center (Palo Alto, CA), Mount Sinai Hospital (New York, NY), and Mayo Clinic (Rochester, MN) between August 1991 and February 2016. The study patients at the three sites were first identified with a diagnosis of HCC using ICD-9 codes. The diagnosis was then confirmed by review of the medical records. Only patients with a new diagnosis of HCC as the primary cancer were included in this study. Cases included consecutive African-American (defined as non-Hispanic African-American) HCC patients identified at the three medical centers during the study period. Caucasian patients (defined as non-Hispanic Caucasian) served as the control cohort and were matched by institution and year of HCC diagnosis (within 6 months) in a 1:1 ratio. The same diagnosis and selection criteria were applied to African-American cases and Caucasian controls. In order to avoid selection bias, our case capture process was to take the first AA meeting our inclusion/exclusion criteria and match them to the first Caucasian who met the inclusion and exclusion criteria using diagnosis year and treatment center. This study was approved by the Institutional Review Board (IRB) at Stanford University (Stanford, CA), Mount Sinai Hospital (New York, NY), and Mayo Clinic (Rochester, MN).

Patient characteristics and outcomes

Information on diagnosis of HCC, viral, and non-viral etiologies (such as alcoholic hepatitis, fatty liver, autoimmune hepatitis, and hemochromatosis) of underlying liver disease, and HCC treatments were obtained by review of laboratory, pathological, radiological, and clinical records. On chart review, the diagnosis of HCC was based on cytology, histology, or imaging (hypervascular lesion $\geq$2 cm on two imaging studies or one imaging study and AFP $>$200, enlarging hypervascular lesion, or lesion $\geq$1 cm with arterial enhancement and venous or delayed-phase washout), regardless of the time point that HCC was diagnosed. Etiology of underlying liver disease(s) was determined by serum markers (e.g., viral hepatitis), diagnostic imaging (e.g., fatty liver), and pathology records. Cirrhosis was determined by standard criteria including histology, imaging (e.g., varices, splenomegaly, and cirrhotic appearance of the liver), laboratory values (e.g., platelet count $<$120,000/μL), or a clinical history of hepatic decompensation (e.g., encephalopathy and ascites).

Information on tumor characteristics was obtained from imaging results. Survival was defined as the time between diagnosis of HCC and either death or last follow-up date. Death and follow-up dates were obtained via chart review. For patients not known to be deceased and whose last visit to the medical center was before May 1, 2015, we performed a National Death Index (NDI) registry search from 1992 to 2015, with a censorship date of May 1, 2015. The NDI is a centralized database of death record information on file in state vital statistics offices with over 90% completion for most states (10). Patients were classified as deceased if documented by chart review or by an NDI search.

Statistical analysis

The continuous variables (age, BMI, laboratory values, etc.) among African-American and Caucasian patients were reported as a mean $\pm$ standard deviation and compared by Student's *t* tests. The Chi-squared tests were used to analyze and compare categorical variables (sex, cirrhosis, ascites, foreign born, etc.) between the two ethnic groups. These variables were reported as a proportion (%). Patient survival was evaluated using Kaplan–Meier methods and the log-rank tests were used to compare survival rates between independent subgroups. The Cox's proportional hazards model was used to obtain unadjusted and adjusted hazard ratios (HR and aHR) and 95% confidence intervals (CI) relating potential predictor variables with survival outcomes.

Survival analyses of subgroups were categorized by year of HCC diagnosis. Year of diagnosis was divided into those diagnosed before 2010 and those diagnosed in 2010 and after. The year 2010 was chosen because equal numbers of African-American and Caucasian patients were diagnosed before and after that year. Cox's proportional hazards models were utilized to determine predictors associated with survival—the variables included in the model were any variable that was significant (p value $<$0.05) from the univariate model in addition to liver disease etiology (HBV, HCV, and other (non-viral)). Stata/SE 11.1 (College Station, TX) was used to perform all statistical analysis. A two-sided p value of less than 0.05 was considered as a threshold for statistical significance.

RESULTS

Patients characteristics

Analysis of the overall cohort. The current study included 578 consecutive African-American diagnosed at the three institutions (36 at Stanford, 457 at Mt Sinai, and 85 at Mayo Clinic) and 578 matched Caucasian patients (36 at Stanford, 457 Mt Sinai, and 85 at Mayo). Patients were matched by year of HCC diagnosis and study site. The majority of cases were diagnosed between 2007 and 2014 (Supplementary Figure 1, see http://links.lww.com/AJG/A29), and the median year of diagnosis was 2010. In 125 out of 1156 patients, HCC was diagnosed by histology or cytology. Most HCC patients were male ($\geq$70%), but a lower proportion of male HCC patients was observed for African-Americans compared to Caucasians (70% vs. 77%, $p = 0.004$). The overall prevalence of cirrhosis was high at 85%, though African-Americans compared to matched Caucasian patients were less likely to have cirrhosis (80% vs. 89%, $p < 0.0001$) or hepatic decompensation (59% vs. 75%, $p < 0.0001$), but were more likely to have higher creatinine levels compared to Caucasians (1.21 vs. 0.99, $p < 0.0001$) (Table 1).

In terms of the underlying liver disease etiology, African-Americans were more likely to have viral etiologies when compared to Caucasians, specifically chronic hepatitis C [(CHC), 93% vs. 65%, $p < 0.0001$], CHC with alcohol (22% vs. 13%, $p < 0.0001$) and chronic hepatitis B [(CHB) 14% vs. 8%, $p < 0.0001$]. Also, compared to Caucasians, African-Americans were more likely to have human immunodeficiency viral infection (HIV) (14% vs. 2%, $p < 0.0001$), and to be co-infected with HIV especially if infected with HCV (HCV/HIV) (11% vs. 1%, $p < 0.0001$). Caucasian patients were more likely than African-Americans to have an underlying etiology related to alcohol (14% vs. 3%, $p < 0.0001$) and fatty liver disease (10% vs. 1%, $p < 0.0001$) (Table 1).

Regarding tumor characteristics, African-Americans had more advanced disease at the time of diagnosis compared to the Caucasian controls (Table 2). They were more likely to have multifocal tumors (39% vs. 32%, $p = 0.014$), vascular invasion (22% vs. 16%, $p = 0.010$), and a larger mean size of the largest tumor (4.7 $\pm$ 3.8 vs. 4.2 $\pm$ 3.5, $p = 0.019$) compared to Caucasian controls. African-Americans were also less likely to have tumor, nodes, metastasis (TNM) stage 1 (34% vs. 68%, $p = 0.003$) and more likely to have TNM stage 3 (35% vs. 5%, $p = 0.004$) at

Table 1 Baseline clinical characteristics of patients with hepatocellular carcinoma in overall cohort

Characteristics	African-American (*N* = 578) % (No.)	Caucasian (*N* = 578) % (No.)	*P* value
Male sex	70% (403)	77% (446)	**0.004**
Average age at diagnosis	60 ± 11 (576)	64 ± 10 (578)	**<0.0001**
Cirrhosis (compensated or not)	80% (396)	89% (453)	**<0.0001**
Decompensated cirrhosis	59% (271)	75% (365)	**<0.0001**
Ascites	30% (144)	41% (222)	**<0.0001**
Encephalopathy	11% (60)	16% (87)	**0.012**
Varices	33% (120)	46% (194)	**<0.0001**
Foreign born	36% (83)	21% (42)	**0.001**
Body mass index	27.2 ± 5.5 (275)	28.5 ± 6.1 (262)	**0.01**
Insurance type			
No insurance	2% (10)	1% (3)	0.06
Private	40% (209)	45% (230)	0.13
Medicare/Medicaid	60% (310)	55% (282)	0.13
Etiology			
Viral hepatitis	93% (529)	65% (364)	**<0.0001**
Chronic hepatitis C	80% (457)	61% (334)	**<0.0001**
HCV/alcohol	22% (127)	13% (73)	**<0.0001**
Chronic hepatitis B	14% (81)	8% (41)	**<0.0001**
HBV/alcohol	2% (12)	1% (6)	0.18
HCV/HBV co-infection	2% (9)	2% (11)	0.60
Alcohol (only)	3% (16)	14% (77)	**<0.0001**
Fatty liver (only)	1% (5)	10% (53)	**<0.0001**
Other	2% (10)	7% (38)	**<0.0001**
Multiple etiologies (other than HCV/alcohol or HBV/HCV)	3% (15)	4% (22)	0.18
Single etiology	73% (412)	81% (429)	**0.01**
HIV			
Total HIV	14% (61)	2% (9)	**<0.0001**
HCV/HIV	11% (49)	1% (6)	**<0.0001**
HBV/HIV	1% (5)	0.2% (1)	0.10
Co-morbidities			
Co-morbidities	67% (377)	66% (363)	0.73
≥3 co-morbidities	13% (74)	18% (97)	**0.04**
Habits			
History of alcohol use	27% (150)	33% (187)	**0.04**
History of tobacco use	50% (272)	48% (268)	0.55
Laboratory values			
Log10 alpha fetoprotein (IQR)	1.8 (1.1–2.8) (530)	1.3 (0.7–2.2) (519)	**<0.0001**
Platelets (in thousands)	155 (89–193) (539)	138 (76–174) (536)	**0.0001**
INR	1.23 ± 0.32 (519)	1.22 ± 0.30 (522)	0.43
Creatinine	1.21 ± 1.15 (540)	0.99 ± 0.51 (534)	**<0.0001**
Alanine aminotransferase	75 (36–92) (536)	74 (34–95) (528)	0.39
Aspartate aminotransferase	115 (54–133) (519)	93 (45–110) (523)	**<0.0001**
Total bilirubin	1.63 (0.6–1.7) (541)	1.73 (0.7–1.9) (539)	0.079

Table 1 (*continued*)

Characteristics	African-American (*N* = 578) % (No.)	Caucasian (*N* = 578) % (No.)	*P* value
Alkaline phosphatase	198 (103–217) (530)	149 (90–176) (530)	**<0.0001**
Albumin	3.40 ± 0.72 (540)	3.58 ± 0.64 (533)	**0.0001**
Child's class			
A	62% (316)	58% (294)	0.13
B	31% (156)	36% (183)	0.08
C	7% (36)	7% (34)	0.80

HCV hepatitis C virus, HBV hepatitis B virus, HIV human immunodeficiency virus, IQR inter quartile range. *P* values less than or equal to 0.05 are bolded

presentation compared to Caucasians, respectively. The majority of patients in both the African-American and the Caucasian groups had BCLC beyond stage A (66% vs. 61%, $p = 0.09$); however, African-Americans had a significantly higher proportion of patients in BCLC stage C (22% vs. 17%, $p = 0.023$). African-Americans also had higher average MELD scores (11.5 vs. 10.8, $p = 0.029$) (Table 2).

Table 2 Tumor characteristics of patients with hepatocellular carcinoma in overall cohort

Tumor characteristics	African-American (*N* = 512) % (No.)	Caucasian (*N* = 516) % (No.)	*P* value
Multifocal tumors	39% (207)	32% (158)	**0.014**
Number of tumors			
1	61% (322)	68% (339)	**0.014**
2	17% (89)	17% (85)	0.91
3	6% (29)	2% (12)	**0.012**
≥4	17% (89)	12% (61)	**0.039**
Average size of largest tumor	4.7 ± 3.8 (507)	4.2 ± 3.5 (487)	**0.019**
Vascular invasion	22% (106)	16% (75)	**0.010**
Metastasis	9% (48)	8% (44)	0.64
TNM			
1	34% (39)	68% (15)	**0.003**
2	16% (18)	9% (2)	0.42
3	35% (40)	5% (1)	**0.004**
4a	8% (9)	0% (0)	0.17
4b	7% (8)	18% (4)	0.09
MELD	11.5 ± 5.5 (512)	10.8 ± 4.5 (519)	**0.0287**
BCLC stage			
B, C, and D	66% (338)	61% (314)	0.09
0	10% (51)	10% (53)	0.87
A	24% (123)	29% (149)	0.08
B	37% (188)	38% (194)	0.77
C	22% (114)	17% (86)	**0.023**
D	7% (36)	7% (34)	0.79

TNM tumor, nodes, metastasis, MELD model for end-stage liver disease, BCLC Barcelona Clinic Liver Cancer. *P* values less than or equal to 0.05 are bolded

African-Americans were also less likely to receive any HCC treatment than Caucasians (84% vs. 89%, $p = 0.010$). The most common treatment in both groups was liver-directed therapy [transarterial chemoembolization (TACE) or radiofrequency ablation (RFA)], but African-Americans were less likely to receive either of these two therapies (58% vs. 72%, $p < 0.001$). Overall, only 3% of African-Americans and 2% of Caucasians underwent liver transplant ($p = 0.24$). Some patients had more than one type of treatment (Table 3).

Analysis by year of diagnosis and ethnicity. The characteristics of the patients diagnosed in year 2010 and after (AA = 288 and Caucasian $n = 292$) remained similar overall (Supplementary Table 1, see http://links.lww.com/AJG/A29). However, among patients diagnosed after 2010, African-American patients were more likely to be younger than 65, have HIV infection, viral etiologies of underlying liver diseases, advanced HCC (BCLC stage C, larger tumors, and vascular invasion), and less likely to receive any treatment (specifically in the BCLC stage A group) compared to Caucasians (Supplementary Tables 1 and 2, see http://links.lww.com/AJG/A29).

Caucasian patients diagnosed after 2010 were less likely to have advanced BCLC stages compared to Caucasian patients diagnosed before 2010 with a 9% reduction in advanced BCLC stages ($p = 0.030$). However, there was no difference in BCLC stages between African-American patients diagnosed before and after 2010 (Table 4). After 2010, there were more Caucasians with stage A compared to African-Americans (32% vs 23%, $p = 0.03$, Supplementary Table 2, see http://links.lww.com/AJG/A29). Also, 12% of African-Americans diagnosed after 2010 had metastasis as compared to 6% of those diagnosed before 2010 ($p = 0.030$) (Table 4).

Caucasians after 2010 experienced a significant increase in the receipt of treatment compared to Caucasians before 2010 ($p = 0.01$). However, receipt of any treatment did not change for African-Americans from before or after 2010 ($p = 0.78$) (Table 4). Caucasians underwent more liver-directed therapy compared to AA (74% vs. 58%, respectively, $p < 0.0001$, Supplementary Table 2, see http://links.lww.com/AJG/A29), though Caucasians after 2010 were less likely to undergo surgical treatment compared with those patients before 2010 (12% vs. 25%, $p < 0.0001$). Notably, Caucasian patients after 2010 also had significantly more co-morbidities (73% vs. 58%, $p < 0.001$) as compared to Caucasian patients before 2010.

Table 3 Initial treatment of hepatocellular carcinoma in overall cohort

Hepatocellular carcinoma treatment	African-American (*N* = 571) % (No.)	Caucasian (*N* = 570) % (No.)	*P* value
Received treatment	84% (480)	89% (510)	**0.01**
Surgical therapy[a]	21% (119)	18% (98)	0.27
Liver-directed therapy[b]	58% (328)	72% (384)	**<0.0001**
Individual treatment types			
Liver transplant	3% (16)	2% (10)	0.24
Resection	18% (103)	16% (88)	0.26
RFA	10% (57)	17% (98)	**<0.0001**
TACE	44% (249)	51% (288)	**0.02**
Sorafenib	7% (38)	5% (29)	0.27

RFA radiofrequency ablation, TACE transarterial chemoembolization. *P* values less than or equal to 0.05 are bolded
[a]Transplant or resection
[b]TACE or RFA

Survival outcomes

Survival analysis of the overall cohort. The overall median (IQR) time of follow-up was 1.96 years (0.59–4.84 years) with an overall 5-year survival of 37%. By ethnicity, the median (IQR) time of follow-up for Caucasians was 1.98 years (0.63–4.88 years) with an overall 5-year survival of 37%, while for African-Americans the median (IQR) follow-up time was 1.95 years (0.55–4.59 years) with an overall 5-year survival of 38%. In total, there was no difference in the 5-year survival rates between African-American and Caucasian patients (38% vs. 37%, $p = 0.712$) (Supplementary Figure 2, see http://links.lww.com/AJG/A29).

Survival analysis by HCC diagnosis year and ethnicity. Long-term survival was significantly better for the cohort diagnosed in 2010 and after compared to the cohort diagnosed before 2010 (40% vs. 33%, $p = 0.009$) (Fig. 1). The median (IQR) follow-up time was 1.58 years (0.36–5.49 years) for the before 2010 cohort and 2.29 years (0.92–4.65 years) for the after 2010 cohort. During the time period before 2010, there was no difference in the 5-year survival rates of Caucasian and African-American HCC patients (36% vs. 32%, $p = 0.61$) (Fig. **2a**). However, for cases diagnosed in 2010 or after, African-American patients had worse 5-year survival than Caucasians (35% vs. 44%, respectively, $p = 0.044$) (Fig. **2b**).

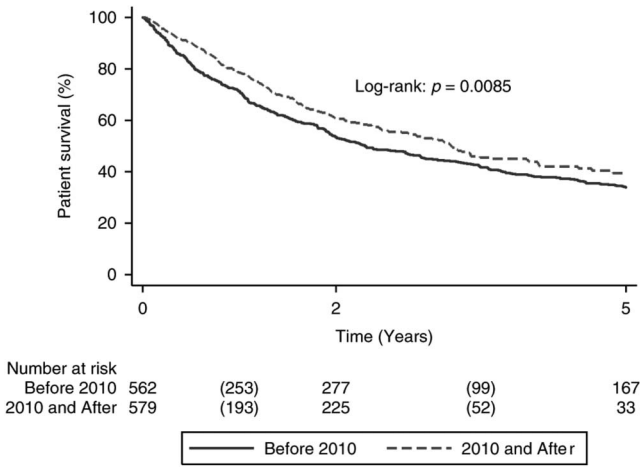

Fig. 1 Five-year survival of all patients with hepatocellular carcinoma compared by hepatocellular carcinoma diagnosis year before 2010 vs. 2010 and after

In Caucasian patients, cases diagnosed after 2010 had better 5-year survival than cases diagnosed before 2010 (44% vs. 32%, $p = 0.003$) (Fig. **3a**); however, among African-American patients, there was no similar improvement of survival over the same time period (35% vs. 36%, $p = 0.50$) (Fig. **3b**). Due to the potential impact of HIV on outcomes, we performed additional analysis to remove all patients with HIV ($n = 70$, 61 African-Americans and 9 Caucasians) and examined survival outcomes without HIV-infected patients in the period 2010 and after. Our original findings remained in which African-American patients had worse 5-year survival compared to Caucasians among the HCC cases diagnosed in 2010 or after, and, in fact, were more significant ($p = 0.034$) (Supplementary Figure 3, see http://links.lww.com/AJG/A29).

Predictors for survival. In univariate Cox's proportional hazards model for patients diagnosed in 2010 and after, significant predictors for increased 5-year mortality were African-American ethnicity, male sex, public insurance, BCLC stages B, C, and D, Child-Pugh score C, alcohol use, and lack of surgical or liver-directed therapy.

On multivariate model for patients diagnosed in 2010 or after, higher 5-year mortality was associated with Child's class C (aHR: 2.05, CI: 1.23–3.41, $p = 0.006$), BCLC above stage A (aHR: 1.75, CI: 1.26–2.43, $p = 0.001$), older age (aHR: 1.03, CI: 1.01–1.04, $p < 0.001$), while undergoing surgical treatment (aHR: 0.09, CI: 0.05–0.16, $p < 0.001$), or liver-directed therapy (aHR: 0.18, CI: 0.12–0.29, $p < 0.001$) were significantly associated with decreased mortality. Neither ethnicity ($p = 0.66$), nor liver disease etiology ($p = 0.19$) were predictors of mortality (Table 5).

For the 2010 and after group, we also reran the multivariate model removing all HIV patients. All mortality predictors stayed the same but increased in association. Specifically, Child's class C (aHR: 2.20, CI: 1.32–3.68, $p = 0.003$); BCLC above stage A (aHR: 1.78, CI: 1.26–2.53, $p = 0.001$); older age (aHR: 1.03, CI: 1.02–1.05, $p < 0.001$); while surgical treatment (aHR: 0.08, CI: 0.04–0.16, $p < 0.001$), or liver-directed therapy (aHR: 0.17, CI: 0.11–0.27, $p < 0.001$) were significantly associated with decreased mortality. Neither ethnicity ($p = 0.22$) nor liver disease etiology ($p = 0.21$) were predictors for survival (Supplementary Table 3, see http://links.lww.com/AJG/A29).

In addition, we performed an interaction analysis between insurance and any treatment to determine if treatment was influenced by insurance, and found that there was no interaction (Supplementary Table 4, see http://links.lww.com/AJG/A29).

DISCUSSION

In this study we aimed to define the clinical characteristics and factors associated with survival among African-Americans and Caucasian patients with HCC. We used a comprehensive database that included key clinical characteristics missing from many of the previous studies. We found that African-Americans were more likely to have viral hepatitis as their underlying liver disease, less likely to have cirrhosis and decompensated liver disease, and more likely to present with advanced HCC stage compared to Caucasians. African-Americans also had higher mortality compared to Caucasians, but only in the group diagnosed after the

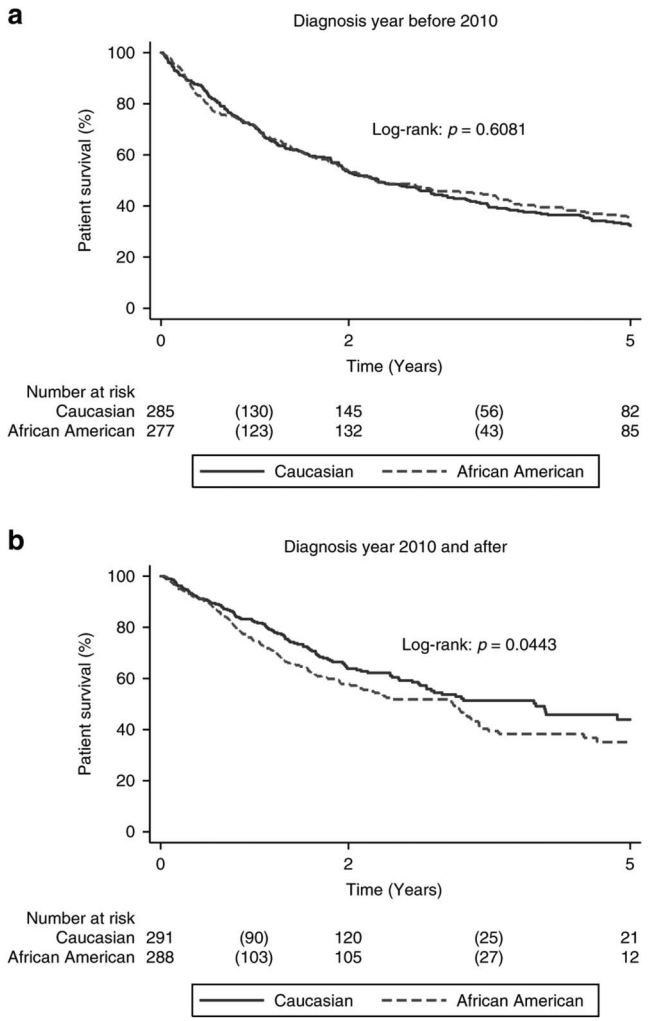

Fig. 2 Five-year survival of patients with hepatocellular carcinoma (HCC) diagnosed before the year 2010 and the year 2010 and after compared by ethnicity (Caucasian vs. African-American). **a** 5-year survival of all patients diagnosed with HCC before the year 2010 compared by ethnicity. **b** 5-year survival of all patients diagnosed with HCC in the year 2010 and after compared by ethnicity

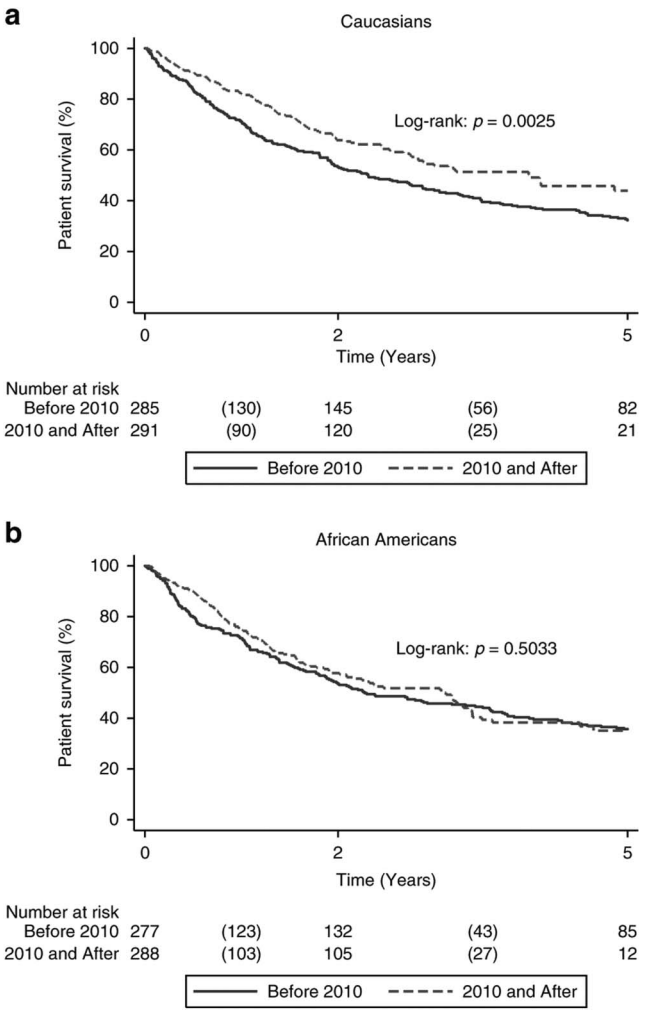

Fig. 3 Five-year survival of Caucasian and African-American patients with hepatocellular carcinoma (HCC) compared by year of HCC diagnosis (before 2010 vs 2010 and after). **a** 5-year survival of Caucasian patients with HCC compared by year of HCC diagnosis. **b** 5-year survival of African-American patients with HCC compared by year of HCC diagnosis

year 2010. This survival difference observed after 2010 was due to increased survival over time for Caucasians but not for African-Americans, which may be related to Caucasians presenting with less advanced HCC at the time of diagnosis and the receipt of significantly more liver-directed therapy with RFA or TACE compared to African-Americans.

We also noted that African-Americans had a significantly higher MELD score compared to Caucasians, which was most likely due to higher creatinine levels in African-Americans, since the calculation of the MELD score is based on bilirubin, INR, and creatinine levels, and there were no differences in INR or bilirubin levels between the two ethnicities. Higher creatinine levels in African-Americans may be a normal finding and not necessarily due to poorer renal function. Jones et al. found that African-Americans have the highest creatinine levels compared to other ethnicities, even among individuals without renal disease (11). Thus, since the MELD score does not adjust creatinine levels accordingly, we chose to use Child's class in the survival prediction model as it is not based on creatinine levels.

The lack of cirrhosis in African-Americans presenting with HCC may be due to a higher proportion of African-Americans presenting with chronic hepatitis B cases, compared to Caucasians, since chronic hepatitis B has been known to cause HCC in the absence of cirrhosis (12). Also, among the chronic hepatitis C patients, African-Americans were less likely to have cirrhosis compared to Caucasians (82% vs. 92%, $p = 0.002$), which is also consistent with a prior study finding, which reported lower rate of cirrhosis among African-Americans with chronic hepatitis C and HCC compared to Caucasians (13).

On the other hand, African-Americans were more likely to have advanced HCC at presentation and were less likely to receive any treatment compared to Caucasians. Previous studies reported similar findings in which African-American patients were more likely to present at more advanced stages (14) with regional and distal metastasis (7) and less likely to receive treatment compared to Asian, Caucasian, and Native American patients, suggesting that African-Americans may be presenting too late in their disease course to be candidates for curative treatment (8).

Table 4 Clinical characteristics of African-American and Caucasian patients with hepatocellular carcinoma patients compared by year of diagnosis

Characteristics	AA Before 2010 (*N* = 277) % (No.)	AA After 2010 (*N* = 288) % (No.)	*P* value	Caucasian Before 2010 (*N* = 285) % (No.)	Caucasian After 2010 (*N* = 292) % (No.)	*P* value
Multifocal	42% (106)	36% (101)	0.15	31% (68)	33% (90)	0.75
Tumor size	4.9 ± 4.0 (238)	4.6 ± 3.7 (268)	0.43	4.5 ± 3.6 (212)	4.0 ± 3.3 (275)	0.12
Vascular invasion	24% (51)	21% (55)	0.39	18% (37)	14% (38)	0.33
Metastasis	6% (16)	12% (32)	**0.03**	8% (22)	8% (22)	0.73
MELD	11.2 ± 5.3 (249)	11.8 ± 5.6 (263)	0.29	11.2 ± 4.7 (244)	10.5 ± 4.2 (275)	0.07
Child's class						
A	59% (144)	65% (172)	0.12	57% (131)	58% (163)	0.73
B	33% (82)	28% (74)	0.19	36% (84)	35% (99)	0.81
C	8% (19)	6% (17)	0.57	7% (16)	6% (18)	0.82
BCLC						
B, C, and D	68% (167)	65% (171)	0.46	66% (155)	57% (159)	**0.03**
0	8% (19)	12% (32)	0.10	9% (21)	11% (32)	0.36
A	25% (61)	23% (62)	0.73	25% (59)	32% (90)	0.08
B	39% (96)	35% (92)	0.33	40% (95)	35% (99)	0.23
C	21% (52)	24% (62)	0.52	19% (44)	15% (42)	0.25
D	8% (19)	6% (17)	0.57	7% (16)	7% (18)	0.85
Treatment						
Received treatment	84% (228)	85% (243)	0.78	86% (238)	93% (271)	**0.01**
Surgical therapy[a]	23% (62)	18% (51)	0.13	25% (61)	12% (36)	**<0.0001**
Liver-directed therapy[b]	58% (158)	58% (165)	0.85	69% (169)	74% (215)	0.21
Sorafenib	3% (9)	10% (29)	**0.001**	3% (7)	8% (22)	**0.01**

AA African-American, MELD model for end-stage liver disease, BCLC Barcelona Clinic Liver Cancer. *P* values less than or equal to 0.05 are bolded
[a]Transplant or resection
[b]Transarterial chemoembolization or radiofrequency ablation

Overall, survival was poor for all patients with HCC with only 37% surviving to 5 years. By comparison, survival analysis showed no difference in survival between African-Americans and Caucasians in the cohort diagnosed before 2010; however, African-Americans had lower survival rates in the 2010 and after cohort. The survival difference appears to be due to an improvement in survival for Caucasians diagnosed after 2010, while survival rates for African-Americans remained unchanged over time.

Though our findings are somewhat similar to a recent population-based study conducted by Momin et al., where they also found that overall, African-Americans had lower survival rates compared to Caucasians (15), we did not find that ethnicity was a significant predictor of mortality. The difference in our study findings may be that we were able to account for HCC and liver disease staging (using BCLC and Child's class), which was not done in the prior study (15). We found, in fact, that it was the advanced presentation of HCC (BCLC beyond stage A and Child's class C) that was the strongest predictor of mortality, not ethnicity. As such, African-American patients diagnosed after 2010 were more likely to have BCLC stage C at the time of HCC diagnosis, as well as being less likely to receive liver-directed treatment compared to Caucasians. Therefore, we suggest one of the main reasons for the difference in survival rates was the advanced stage of disease found in African-Americans when compared to Caucasians in the 2010 and after cohort, which may have affected the type of treatment received. Interestingly, Caucasians received less surgical treatment after 2010 as compared to before 2010 despite having lower HCC staging in the post 2010 time period. However, more Caucasian patients diagnosed in 2010 or after had co-morbidities as compared to Caucasian patients before 2010, and this may have contributed to the lower rate of surgical treatment in the after 2010 group (16). Nevertheless, Caucasians received more liver-directed therapy after 2010 compared to AA (74% vs. 58%, $p < 0.001$). Thus, the survival advantage seen in Caucasians after 2010 may have been due to less advanced HCC presentation and more liverdirected therapy.

Discovering cancer at an earlier stage is a modifiable problem if HCC surveillance methods and/or adherence to HCC surveillance guidelines can be improved. However, there are barriers that must be overcome in order to improve surveillance. First, studies have found that African-Americans do suffer from poor linkage to care for their primary liver disease leading to inadequate screening and surveillance for HCC itself (17–23). One study reported HCC surveillance rates as low as 17% in cirrhotic patients diagnosed with HCC between 1994 and 2002 (17). Higher surveillance rates were found for Asians, younger patients,

Table 5 Multivariate Cox proportional hazards model for 5-year mortality risk among patients diagnosed in the year 2010 or after

Clinical characteristics	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Race				
Caucasian	1 (Referent)			
African-American	1.29 (1.01–1.66)	**0.045**	1.07 (0.78–1.48)	0.66
Male	1.34 (1.00–1.80)	**0.047**	1.26 (0.90–1.78)	0.18
Age	1.01 (1.00–1.03)	0.091	1.03 (1.01–1.04)	**<0.001**
Insurance				
Medicare/ Medicaid	1 (Referent)			
Private	0.76 (0.58–0.99)	**0.042**	0.84 (0.62–1.13)	0.25
Alcohol use	1.48 (1.14–1.92)	**0.004**	1.30 (0.95–1.78)	0.10
HCC staging				
BCLC stages				
0 and A	1 (Referent)			
B, C, and D	2.45 (1.84–3.27)	**<0.001**	1.75 (1.26–2.43)	**0.001**
Child-Turcotte-Pugh score				
A and B	1 (Referent)			
C	2.75 (1.80–4.20)	**<0.001**	2.05 (1.23–3.41)	**0.006**
Treatment				
No treatment	1 (Referent)			
Surgical therapy[a]	0.09 (0.06–0.16)	**<0.001**	0.09 (0.05–0.16)	**<0.001**
Liver-directed therapy[b]	0.18 (0.12–0.25)	**<0.001**	0.18 (0.12–0.29)	**<0.001**
Liver disease etiology				
Non-viral	1 (Referent)			
Hepatitis B viral infection	1.03 (0.58–1.83)	0.93	0.59 (0.27–1.30)	0.19
Hepatitis C viral infection	0.95 (0.69–1.29)	0.73	1.29 (0.88–1.89)	0.19

CI confidence interval, ***HCC*** hepatocellular carcinoma, ***BCLC*** Barcelona Clinic Liver Cancer. *P* values less than or equal to 0.05 are bolded
[a]Transplant or resection
[b]Transarterial chemoembolization or radiofrequency ablation

patients living in zip codes with higher income or education, and seeing a specialist (hepatologist or gastroenterologist), while the lowest rates were found for African-Americans (17).

Second, HCC surveillance can be less vigorous in chronic hepatitis B (CHB) patients (which was more common in African-Americans) since CHB patients are less likely to have cirrhosis before the development of HCC. Thus, providers may fail to order surveillance tests due to unrecognized liver disease and lack of cirrhosis. Furthermore, patients may not be seeking care until late in the course of their liver disease due to lack of symptoms (18–20).

Therefore, to overcome these potential barriers to care, awareness of the risk factors for liver disease and its associated outcomes must be reinforced for practitioners while other surveillance methods must be applied to community settings to capture those most at risk for liver disease (14,17–19).

Earlier studies were also unable to account for differences in liver disease etiology and its impact on HCC survival (15). We found that liver disease etiology was not a significant predictor for survival even when we removed all patients that were infected with HIV and performed additional survival analysis without HIV patients. In fact, removing HIV patients only strengthened our findings that it was mainly cancer staging that accounted for increased mortality in African-Americans.

There were some limitations of our study with many inherent in its retrospective design. However, our primary study outcome was overall survival, which is an objective outcome comprehensively collected by both patient record review at each study site and also by the National Death Index search. The other limitation is the potential bias toward shorter follow-up time for the 2010 or after group, especially with regard to 5-year survival. However, the median follow-up time for the 2010 or after group was 2.29 years and not shorter than the median follow-up for the former group (1.58 years), which is likely adequate for a lethal disease such as HCC. In addition, our study results were similar to a population-based study suggesting that the limitations of the study design are compensated by using data from multiple sites. We tried to take into consideration potential geographic differences by including three sites at different states (California, Minnesota, and New York).

Another limitation is the uneven distribution of cases among the three study centers with more than half of the patients coming from one of the three centers in our study, but we matched the Caucasian HCC controls to African-American HCC cases according to institution to minimize the potential effects of differences in local resources and treatment preferences. Also, the ethnic distribution of patients at each center reflects the ethnic distribution, where the centers are located. For example, there are more AAs in New York City, where Mt Sinai is located, compared to the areas where Stanford and Mayo Clinic are located (24–26). Selection bias may also arise due to the missing data especially for tumor characteristics. However, the total percent of patients missing tumor characteristics was only 11%, and the percent missing for both groups was approximately equal, so if there is a selection bias, it appears that it is symmetrical in bias. Finally, we were not able to assess for adherence to HCC surveillance guidelines in this study. Future studies addressing the impact of HCC surveillance on survival difference between AAs and Caucasians are needed.

In conclusion, 5-year survival for patients with HCC remains poor. However, long-term survival improved over time for Caucasians with HCC, but not for their African-American counterparts resulting in a survival difference between the two ethnic groups, though ethnicity was not a predictor of HCC mortality. Rather it appears that staging of HCC was the most significant factor for survival. We found that though African-American HCC patients presented with less cirrhosis, they had larger tumors with more vascular invasion, were more likely to have BCLC stage C, and were thus less likely to receive curative

treatment. More studies are needed to better understand why African-Americans are presenting at late stages in their liver disease.

CONFLICTS OF INTEREST

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Specific author contributions: Study design: JE, MN, LR, and MS. Data collection: JE, JY, JL, PN, NG, LR, MS, and MN. Data analysis: JE and MN. Manuscript drafting and/or revision: JE, RC, and MN. Data interpretation and manuscript review: all authors. Study concept and supervision of study: MN.
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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ African-Americans have higher hepatocellular carcinoma (HCC) incidence and mortality compared to Caucasian patients.
- ✓ African-Americans with HCC have the poorest long-term survival.

WHAT IS NEW HERE

- ✓ HCC survival improved over time for Caucasians but not African-Americans.
- ✓ Survival was similar between African-Americans and Caucasians with HCC before 2010 but worse in African-Americans after 2010.
- ✓ Advanced HCC was an independent risk factor for HCC mortality, but not ethnicity.

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