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Hepatitis C Positive Black Patients Develop Hepatocellular Carcinoma at Earlier Stages of Liver Disease and Present with a More Aggressive Phenotype

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Abstract

Background and Aims: In the United States, mortality after a diagnosis of hepatocellular carcinoma (HCC) is higher in patients who are Black than in patients of other racial groups. We aimed to clarify factors contributing to this disparity by analyzing liver and tumor characteristics in patients with HCC and a history of hepatitis C virus (HCV) infection.

Methods: Records of HCV/HCC patients at our institution, 2003–2018, were reviewed retrospectively. Race/ethnicity was self-identified. Imaging, laboratory, and pathological features were compared between Black and non-Black cohorts.

Results: Among 1195 individuals with HCC, 390 identified as Black. At HCC diagnosis, Black patients had better liver function, as measured by Child-Pugh score, model of end stage liver disease score, histology of non-tumor tissue, and fibrosis-4 (FIB-4) score (all $p < 0.05$). FIB-4 scores were <3.25 in 31% of Black patients. In addition, Black patients had less early stage HCC (20.2% vs. 32.3%, $p<0.05$); larger tumors [median, interquartile range (IQR), 3.5 (2.2–6.2) cm vs. 3.1 (2.1–5.1) cm, $p<0.01$]; more multiple tumors [median, IQR, 1 (1–3) vs. 1 (1–2), $p=0.03$]; more poorly differentiated tumors (30.3% vs. 20.5%, $p<0.05$); and more microvascular invasion (67.2% vs. 56.5%, $p<0.05$).

Conclusion: Black patients with HCV exposure develop HCC at earlier stages of liver disease than members of other racial groups. Nearly one-third would not qualify for HCC screening using the common FIB-4 cirrhosis threshold. Practice guidelines which stress HCC surveillance for

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cirrhotic HCV patients may need to be revised to be more inclusive for Black patients. In addition, tumors in Black patients carry worse prognostic features; molecular studies are needed to characterize their biological properties.

Keywords

hepatocellular carcinoma; Black race; cirrhosis; disparities; hepatitis C virus; surveillance

Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of site-specific cancer-related death around the world[1]. According to the National Institution of Health Surveillance, Epidemiology, and End Results (SEER) database, age-adjusted HCC incidence tripled between 1975 and 2005, from 1.6 per 100,000 to 4.8 per 100,000 in the United States (US)[2]. In 2012 age-adjusted HCC incidence rates were 6.7/100,000[3]. In the latest annual report on the status of cancer in the US published in 2020, the cross-sectional incidence (2012–2016) and death (2013–2017) rates of primary liver cancer were increasing[4], although the rate of increase was slowing[5]. HCC disproportionally affects racial/ethnic minorities in the US: during 2005–2007, the HCC incidence in the Black population was 1.5-fold higher than in the generalpopulation[6]. Hepatitis C virus (HCV) infection is the leading risk factor for liver cancer in the US[7,8] and also effects communities disproportionately: the estimated prevalence of HCV in the general population is 1.67% (95% CI 1.53–1.90)[9], compared to 2.2% among Black individuals and 1.3% among non-Hispanic White individuals[10].

The 5-year relative survival rate for liver cancer diagnosed between 2009 and 2015 was 18%, with large differences depending on the tumor status at the time of diagnosis; it was 33% for patients with localized tumors versus 3% for patients with extrahepatic metastases[11]. Many patients are diagnosed with advanced HCC and receive only palliative treatment; however, early stage HCC can be cured surgically. The 5-year survival rate for patients who had surgery for early stage HCC was 50%, underscoring the importance of early detection at a potentially curative stage[12].

Black patients with HCC have the lowest overall survival of any racial/ethnic group[13,14]. The reasons for this disparity are incompletely understood but are likely multifactorial and may include socioeconomic factors and differences in access to care[15,16], as well as possible differences in tumor biology. Black individuals are less likely to receive curative treatment than members of other racial groups [17]. Screening for HCC occurs less frequently among Black patients than among other racial/ethnic groups[18], which may increase the chances that diagnosis will be delayed until after HCC has reached an advanced stage, thereby increasing mortality.

In the Western world, up to 90% of HCCs arise in a cirrhotic liver[19]. Because cirrhosis is such a strong HCC risk factor, practice guidelines of the American Association for the Study of Liver Disease (AASLD)[20,21], the European Association for the Study of Liver Disease (EASL)[22], and the Asian Pacific Association for the Study of Liver Disease (APASL)[23] recommend twice-annual HCC surveillance for patients with cirrhosis. Surveillance is considered to be cost-effective for groups of patients in whom the annual HCC incidence is

≥ 1.5% per year[24]. Patients with biopsy-diagnosed bridging fibrosis (Metavir F3) are also at elevated risk for developing HCC[25]. Accordingly, EASL recommends HCC surveillance for patients with bridging fibrosis in addition to patients with definite cirrhosis[22]. The FIB-4 score is a non-invasive alternative to biopsy: a value of FIB-4 >3.25 correlates with advanced fibrosis and cirrhosis[26] and has a positive predictive value of 82% with specificity of 98% for diagnosing cirrhosis[27].

Data suggest that Black patients at high risk for developing HCC may be less likely to meet commonly accepted criteria for HCC surveillance than members of other racial/ethnic groups. HCV-associated hepatic fibrosis progresses more[28] slowly in Black individuals than White patients. In the Veterans Administration HCV Clinical Case Registry, non-Hispanic Black patients were less likely to have cirrhosis than White or Hispanic patients (HR = 0.58, 95 % CI = 0.55 – 0.60)[28]. Consistent with this, a small study from our group showed that Black patients have better liver function at diagnosis of HCC than other groups[29]. Similar findings were published by Jones et al.,[30] who analyzed HCC in cirrhotic patients who had a variety of underlying liver diseases. They found that Black patients with HCC had better liver function, but worse tumor characteristics and the shortest survival of any group examined. Because HCC surveillance programs often focus on patients with cirrhosis, any group that tends to develop HCC without first developing cirrhosis may be less likely to receive HCC screening, increasing the likelihood of delayed HCC diagnosis.

To better understand the excess HCC-related mortality in the Black population, we aimed to compare liver function and presence of cirrhosis at the time of HCC diagnosis in Black versus non-Black patients with a history of HCV infection. Secondarily, we aimed to investigate whether HCC in Black patients with a history of HCV is associated with a more aggressive phenotype, as a potential biological contributor to excess mortality.

Materials and methods

Approval for this retrospective study was obtained from the Institutional Review Board of the Icahn School of Medicine at Mount Sinai with a waiver of informed consent. All patients with a history of HCV infection who were diagnosed with HCC at the Mount Sinai Hospital from 2003 to August 2018 were included.

Study population

An initial list of patients was generated using the ICD-9 code 155.0, and a manual review was performed to confirm HCC, as defined by accepted radiographic and/or pathologic criteria. Patients with a history of HCV infection were defined as having tested seropositive for HCV antibody and/or HCV RNA and/or having a recorded HCV genotype. Race and ethnicity were self-identified. Individuals were initially classified as belonging to one of the following groups: white non-Hispanic, Black non-Hispanic, Asian and Pacific Islanders, persons of any race who identified themselves as having Hispanic ethnicity, and others. For data analysis, these groups were collapsed into non-Hispanic Black and all others.

Clinicopathological variables

Demographic, clinical, and socioeconomic factors including age, gender, body mass index (BMI), and type of insurance, were collected. Government-insured patients were defined as those with Medicare and no supplemental insurance, or Medicaid. Commercially insured patients were defined as those with non-government-subsidized insurance or Medicare plus a supplemental private insurance carrier. Infection with human immunodeficiency virus (HIV) or exposure to hepatitis B virus (HBV) was recorded. Chronic (on-going) HBV infection was defined as the presence of hepatitis B surface antigen (HBsAg) and/or HBV DNA in serum with or without hepatitis B core antibody (anti-HBc^{+}). HBV exposure was defined as the presence of at least one of the three following serum factors: hepatitis B core antibody (anti-HBcAb), HBsAg and/or HBV DNA. HIV infection was defined was defined by the presence of HIV RNA and/or anti-HIV antibodies in serum. Any history of HCV treatment (interferon, ribavirin, interferon + ribavirin, direct-acting antivirals, or interferon/ribavirin plus direct-acting antivirals) was recorded. Sustained virologic response (SVR) was defined as aviremia 24 weeks after completion of HCV treatment.

Laboratory variables

Laboratory data included platelet (PLT) count, albumin, total bilirubin, international normalized ratio (INR), and α-fetoprotein (AFP). Values from the date closest to HCC diagnosis were used. Liver function and cirrhosis were determined using MELD score, Child-Pugh classification, and FIB-4 index score, a validated non-invasive tool to estimate hepatic fibrosis stage. FIB-4 is calculated as: age (years) X aspartate aminotransferase (U/L) / platelets (10^{9}) alanine aminotransferase (U/L).

Imaging variables

Imaging data at the time of diagnosis of HCC were collected. Imaging modalities included abdominal contrast-enhanced computerized tomography (CT) and magnetic resonance imaging (MRI). The assessment of cirrhosis and portal hypertension included evidence of liver surface nodularity, morphology and size of the liver (left lobe and caudate hypertrophy or small size of the liver), presence of ascites, varices or splenomegaly. Mentions of “cirrhosis” and “portal hypertension” in CT/MRI reports were recorded.

Tumor characteristics on imaging included tumor size, defined as largest dimension of the largest tumor, tumor number and location, and macrovascular invasion (defined as portal vein or hepatic vein thrombus), and presence of metastases at diagnosis. Barcelona Clinic Liver Cancer (BCLC) staging and Milan criteria at diagnosis were also determined based on the imaging and laboratory data.

Pathological variables

For patients who had resection or transplantation and a pathology report, we recorded the METAVIR scores of the non-tumor liver parenchyma[31,32]. The METAVIR system classifies the stage of fibrosis on a five-point scale, F0=no fibrosis, F4=cirrhosis, and histological activity on a four-point scale, A0=no activity, A3=severe activity. Data on tumor characteristics was also collected, including tumor size, number, differentiation, necrosis,

presence of dysplastic nodules and satellite lesions, microvascular invasion, gross vascular invasion, tumor necrosis, tumor margins resection, and TNM 8th edition staging.

Statistical analysis

Data were analyzed with the Statistical Package for the Social Sciences (SPSS) version 22.0 using a significance level of 0.05. Chi square or Fisher's exact tests were used for categorical data and the Mann–Whitney-U test was used for continuous data. Survival was estimated using Kaplan-Meier analysis and compared using the log-rank.

Results

Study group

Between 2003 and 2018, 1195 patients with HCC and a history of HCV infection where managed in our hospital. Within this group, 390 individuals self-identified as non-Hispanic Black. The remaining group of 805 patients was comprised of individuals who identified as non-Hispanic white (n=406), Hispanic (n=221), Asian/Pacific Islander (n=80), other (n=16), and unknown (n=82) (Figure 1, Table 1). The majority was male; the distribution of gender did not differ between Black patients and other patients. Black patients were slightly older at HCC diagnosis (median age 62 vs. 59 years, $p<0.01$), had slightly lower body mass index (BMI) (26.3 vs. 26.9 kg/m^2, $p<0.01$), and were less likely to have commercial insurance (25.9% vs. 40%, $p<0.01$). A total of 497 patients had current active HBV infection and/or previous exposure to HBV, as indicated by serum positivity for HBsAg and/or HBV DNA and/or HBc antibodies; 52 patients had chronic HBV infection and 196 patients had HIV infection. HIV infection and chronic HBV infection/HBV exposure were more prevalent in Black patients than in others (HIV: 23.3% vs. 13.2%, $p<0.01$; HBV: 49.3% vs. 59.3%, $p<0.01$). At the time of HCC diagnosis, 81 patients had been cured of HCV, with a similar proportion in Black and non-Black groups. Among 395 patients who underwent surgery and had an available pathology report, 238 patients underwent resection and 157 had a liver transplant; the distribution of surgical procedure type was similar in Black and non-Black cohorts (Figure 2).

Liver function, fibrosis stage, and Childs Class at HCC diagnosis

The extent of liver disease at HCC diagnosis was evaluated by analyzing laboratory, imaging and pathology data. As indicated in Table 3, at HCC diagnosis, Black patients had better liver function and less liver injury than non-Black patients, with a higher median platelet count (144 vs. 105 $*10^3/mm^3$, $p<0.01$), lower median INR (1.1 vs. 1.2, $p<0.01$) and lower median bilirubin level (0.90 vs. 1.2 mg/dL, $p<0.01$). Black patients were more likely to have Child-Pugh class A cirrhosis than the remainder of the cohort (69.4% vs. 58.5%, $p<0.01$), and were 2-fold less likely to have Child-Pugh C cirrhosis (5.9 vs. 12.9%, $p<0.01$). Black patients' median MELD score was lower (9.0 vs. 10, $p<0.01$), as was their FIB-4 score (4.66 vs. 6.54, $p<0.01$), which is particularly notable because the median age of Black individuals was higher; all other factors being equal, the FIB-4 increases with the age of the patient. Thirty-one percent of Black patients had a FIB-4 score <3.25 at the time of HCC diagnosis. Consistent with these findings, among 339 patients with histopathological data, Black patients had less advanced liver disease in the non-tumor tissue: 35% did not have cirrhosis

(cirrhosis is defined as METAVIR F-4) and 20% had METAVIR F-0–2. The grade of inflammation was similar in both groups (Table 2).

Imaging data also indicated that Black patients had less advanced liver disease (Tables 3 and 4). They were less likely to have a liver with a nodular contour (49.7% vs. 78.5%, $p<0.01$) and less likely to have a liver with altered morphology, as indicated by hypertrophy of the left lobe or small overall size ($p<0.01$). Portal hypertension was reported in 20% of Black individuals vs. 55% in non-Black individuals ($p<0.01$). Black patients were less likely to have ascites, varices, and splenomegaly ($p<0.05$ for all). Only 50% of the imaging reports of Black patients mentioned “cirrhosis” versus 79% of non-Black patients and mild cirrhosis was noted more frequently (8.9% vs. 4.1%, $p<0.01$).

Tumor characteristics and prognosticators

At the time of HCC diagnosis, Black patients had more advanced and less curable disease. On imaging, tumors in Black patients were on average larger and more frequently multifocal, bilateral, with gross vascular invasion (thrombus in portal vein or hepatic vein), were more likely to be metastatic (Table 5), and a smaller percentage were within Milan criteria ($p=0.04$). There was a statistically significant difference in Barcelona Clinic Liver Cancer staging between Black patients and the remainder of the cohort ($p<0.01$). Despite more advanced HCC, Black individuals had lower AFP levels; 30% had AFP <10 ng/ml. On pathology, tumors in Black patients were more likely to be poorly differentiated (30.3% vs. 20.5% $p<0.05$) and to show microvascular invasion (67.2% vs. 56.5%, $p=0.04$) (Table 6). The prevalence of dysplastic nodules and satellite lesions was higher in the Black patient cohort. A lower percentage of Black patients had early stage (T1) disease (20.2% vs. 32.2% $p<0.05$). The groups were comparable in the prevalence of tumor necrosis.

The impact of HBV and HIV

Patients with HBV exposure (i.e., positive for one of more HBV proteins and/or DNA and/or HBc antibody) had worse tumor characteristics; these patients were less likely to be within Milan criteria, and their tumors were larger, a higher percentage were > 2.5 cm in diameter, and tumors were more likely to be multifocal. A subgroup analysis was performed in order to assess whether some of the unfavorable characteristics of HCC in Black patients were due to their higher prevalence of HBV exposure and the unfavorable characteristics of HBV-associated HCC. A comparison between Black patients with HBV exposure and non-black patients with HBV exposure demonstrated that the Black patients had less liver fibrosis at the time of HCC diagnosis [median FIB-4, IQR; 4.5 (2.8–8.3) vs. 6.9 (4.4–11), $p<0.01$] and worse tumor characteristics, defined as larger tumors, multiple tumors and a smaller percentage within Milan criteria (Table 7). Because all the patients in this sub analysis had a history of HBV exposure, the difference between Black and non-Black patients cannot be attributed to a difference in the prevalence of HBV exposure.

HIV-positive patients had better liver function tests, less liver fibrosis and better tumor characteristics at the time of HCC diagnosis than patients without HIV exposure. The HIV-positive patients had smaller tumors and were more commonly within Milan criteria. The

more favorable tumor characteristics were far more apparent in HIV-positive non-Black patients than in HIV-positive Black patients (Table 8).

We performed a sub-analysis of 431 patients who did not have any indication of HIV or HBV exposure; patients were excluded if their records lacked data about possible exposure to these two viruses (Table 9). In this sub analysis, Black patients (n=117) were younger and less likely to have commercial insurance than the remainder of the cohort. They had higher platelet counts, lower bilirubin levels and lower MELD scores, but were less likely to be within Milan criteria, less likely to have TMN stage 1 disease and more likely to have extrahepatic metastases, and microvascular invasion (all $p \leq 0.05$).

Long term survival

Survival analysis was performed on 780 patients who had at least five years of follow-up data. Black patients had shorter overall median survival: 18 months (IQR, 6–67 months) vs. 30 months (IQR, 9–90 months) $p<0.01$. Five-year survival was 21% in Black patients, and 28.4% in the remainder of the cohort, $p=0.02$; one-year survival did not differ between groups (Figure 3).

Discussion

This study uncovered two striking features of HCC in Black patients with a history of HCV infection that exposure may contribute to the known higher HCC-related mortality in this demographic group. At the time of HCC diagnosis, liver fibrosis was significantly less advanced in Black patients, and yet their tumors were more advanced in stage and had worse pathologic prognostic features than those of non-Black patients. Black individuals had lower median survival and lower five-year survival, despite having better liver function at the time of HCC diagnosis. Our findings indicate that HCC in Black patients often has characteristics associated with a more aggressive disease course. Features of aggressive HCC include vascular invasion, greater tumor size and poor differentiation[33,34]. Black patients in our study presented with larger tumors and a higher prevalence of multiple tumors, gross and microvascular invasion, and poorly differentiated tumors. More aggressive tumor biology is associated with poor outcomes in Black individuals with other types of cancer, including endometrial cancer[35], prostate cancer[36] and breast cancer; Black women have more aggressive breast cancer, and a higher prevalence of triple-negative tumors[37]. Because HCC tumors in our Black cohort were larger, more likely to be multifocal, and with vascular invasion, Black patients were less likely to be within Milan criteria, limiting treatment options.

It is unclear to what extent these characteristics reflect a distinctive molecular profile that confers an inherently more aggressive phenotype and to what extent they reflect diagnosis at a more advanced stage of disease, due to delayed diagnosis. Black patients were less likely to have commercial insurance, as found in previous studies[21], raising the possibility that barriers to accessing healthcare services may have contributed to delays in HCC diagnosis. However, they were also likely to meet screening criteria, and thus they and their providers may have thought that screening was not necessary.

In this study, Black patients developed HCC at earlier stages of liver fibrosis than other racial groups. According to AASLD guidelines, patients with cirrhosis should have life-long twice-annual HCC surveillance[20,21]. As previously described, a value of FIB-4 greater than 3.25 correlates with advanced fibrosis and cirrhosis[26.27]. Nearly one-third of the Black patients in our cohort had a FIB-4 score less than 3.25. Because of this, their need for HCC surveillance may have been underestimated by the patients and their healthcare providers. Moreover, half of the Black patients did not have any features of cirrhosis on imaging which could have been another trigger for HCC screening by the healthcare provider. Practice guidelines which recommend HCC surveillance for cirrhotic HCV patients may need to be expanded to serve the needs of Black patients.

AFP is a well-established HCC biomarker. A prospective randomized trial of HBV-positive patients conducted in China showed that a surveillance program using AFP and liver ultrasound performed every 6 months resulted in a 37% reduction in HCC mortality. As has been noted previously, Black patients with HCC have lower levels of AFP[40]. Our findings corroborate this finding; one-third of the Black patients had AFP values below 10 ng/mL. Thus, surveillance guidelines that rely on AFP may not be optimal for Black patients and reliance on this test could contribute to delays in HCC diagnosis in the Black population.

The prevalence of co-infection with HIV and previous HBV infections was higher in Black individuals. The effect of HBV exposure on HCC risk in patients with a history of HCV infection has not been resolved[41–44]. Kubo et al.[45] reported that HCC was more likely to develop in non-cirrhotic livers in patients with HCV RNA and anti-HBc antibody than in patients with HCV RNA and no evidence of HBV exposure. Matsuoka et al[42] demonstrated that HCV-infected patients with anti-HBc antibodies and no other indication of HBV infection had greater fibrosis stage than patients with no HBV exposure. Other studies found no association between prior HBV infection and liver fibrosis stage[46]. In our study, patients with HBV exposure have higher scores for fibrosis stage. Kubo et al.[45] reported that patients with HCV and anti-HBc antibodies had less well differentiated tumors, but tumors were similar in size. In our study, patients with prior HBV infection had larger tumors and a lower percentage were within Milan criteria. This finding suggests that Black patients with a history of HCV and HBV infection may require especially vigilant HCC surveillance.

In our study, HIV-positive patients had better liver function and more favorable tumor characteristics than HIV-negative patients, which differs from results in studies performed during the early years of antiretroviral therapy[47]. Perhaps our findings of better liver function at HCC diagnosis reflect better screening in HIV-positive patients that occurred because these patients are more engaged with healthcare; unfortunately, the more favorable disease features were much more apparent in non-Black patients than in Black patients.

In a subset analysis of patients with neither HBV nor HIV exposure Black individuals had less advanced liver disease than non-Black individuals at the time of HCC diagnosis, but had their HCCs had worse prognostic features, indicating that the HCC profile identified in this study (i.e., relatively well-preserved liver function and more aggressive tumors) is characteristic of HCC in HCV-infected Black patients and is not due to the higher prevalence of HBV and/or HIV exposure in this group. Future research should investigate the molecular

biology of this profile and seek to identify HCC risk factors in non-cirrhotic livers, specifically exploring germline and somatic mutations[46–50], toxic exposures (air pollution, alcohol [51] and cigarette smoke[52]) and co-morbidities, such as type II diabetes[53,54].

Our single-site retrospective study has several limitations, including possible selection bias and an inability to establish causality; however, our findings are consistent with those reported previously[39]. Cirrhosis was identified by FIB-4 scores and imaging data in most cases; however, the available biopsy data supported the conclusion that Black individuals had less advanced fibrosis. Additionally, our survival analysis included patients with coinfection of HIV and HBV and this could be a cofounder of the survival differences.

In conclusion, we describe a novel profile of HCC in Black patients with HCV where in patients present with less fibrosis progression, but with more advanced tumors that have more aggressive pathologic features. This profile was present in the study group as a whole and in the subgroup of Black patients who did not have any prior exposure to HIV or HBV. These findings provide a foundation for designing studies to define the molecular signature(s) of HCC in Black individuals and to identify any mutations/subtype that may guide targeted treatment. Our results also reveal the need to revise current HCC surveillance criteria to include non-cirrhotic Black patients with a history of HCV exposure, thereby ensuring that these guidelines serve the needs of the Black patient population.

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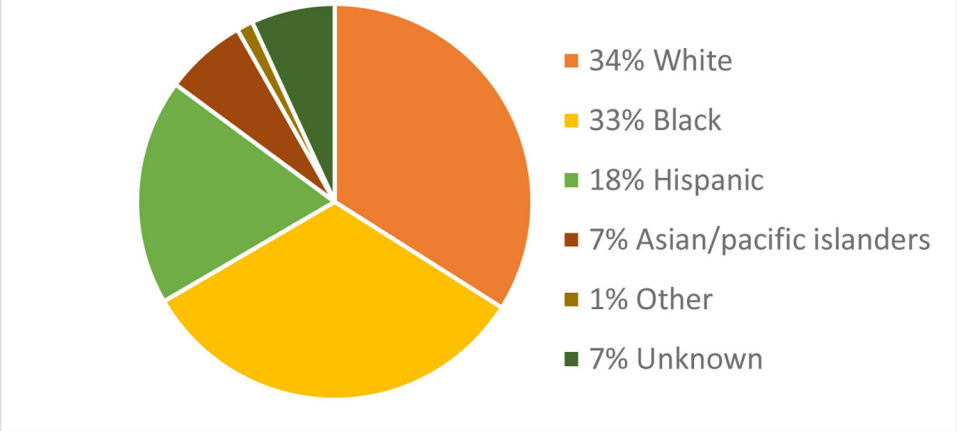

Figure 1.
Patients with chronic hepatitis C virus and hepatocellular carcinoma: distribution of racial/ethnic groups

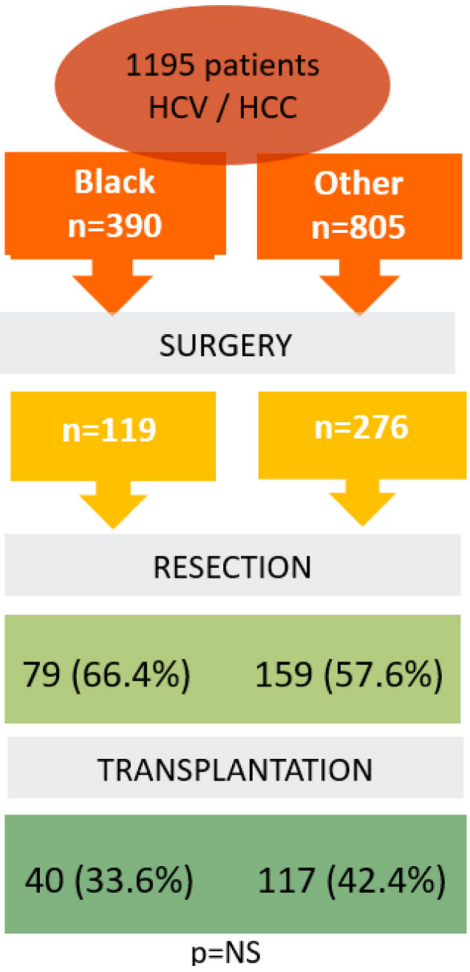

Figure 2.
Distribution of surgical treatment and type of surgery among black and other racial/ethnic groups

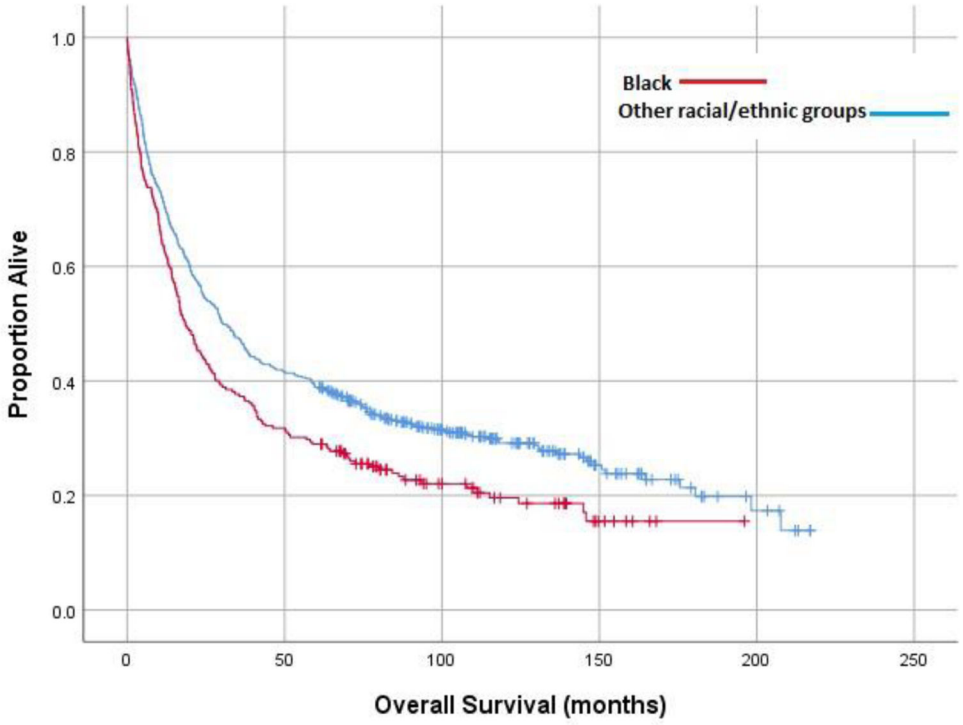

Figure 3.
Overall survival black and other racial/ethnic groups, Kaplan–Meier curves ($p<0.01$)

Table 1:

Patients Characteristics:

		Non-Black N=805	Black N=390	P value
Gender	**Male**	621 (77.1%)	288 (73.6%)	NS
	Female	184 (22.9%)	102 (26.2%)	
Age, median (IQR)		59 (54–66)	62 (57–67)	<0.01
BMI, median (IQR)		26.91 (24.02–30.30)	26.30 (22.65– 29.59)	<0.01
Commercial Insurance		326 (40.4%)	101 (25.9 %)	<0.01
Chronic HBV[a] co-infection		29 (3.6%)	23 (5.9%)	0.07
Previous HBV exposure		285 (49.3%)	212 (59.3%)	<0.01
HIV[b] co-infection		106 (13.2%)	90 (23.3%)	<0.01
HCV[c] treatment SVR[d]		55 (6.7%)	27 (7%)	0.954

[a]HBV – Hepatitis B virus

[b]HIV – Human Immunodeficiency Virus

[c]HCV – hepatitis C virus

[d]SVR – Sustained Virologic Response

Table 2:

Pathological liver disease staging and grading

		Non-Black N=233	Black N=106	P value
Pathological inflammatory activity grading (N=339)	1	33 (14.2%)	20 (18.9%)	0.230
	2	169 (72.5%)	79 (74.5%)	
	3	29 (12.4%)	7 (6.6%)	
	4	2 (0.9%)	0	
Pathological liver fibrosis staging (N=339)	1	4 (1.7%)	2 (1.9%)	<0.01
	2	17 (7.3%)	21 (19.6%)	
	3	25 (10.7%)	15 (14.0%)	
	4	187 (80.3%)	68 (63.6%)	

Table 3:

Liver Function on Diagnosis (Laboratory and histology)

		Non-Black N=805	Black N=390	P value
CHILD PUGH score	A	466 (58.5 %)	270 (69.4%)	<0.01
	B	231 (28.9%)	96 (24.7%)	
	C	103 (12.9%)	23 (5.9%)	
MELD score[a], median (IQR)		10 (7–16)	9 (7–14)	0.02
FIB-4[b] score, median (IQR)		6.54 (3.99–10.53)	4.66 (2.94–7.52)	<0.01
FIB-4 score < 3.25		143 (17.8%)	122 (31.1%)	<0.01
Total bilirubin (mg/dL), median (IQR)		1.20 (0.7–2.2)	0.90 (0.60–1.50)	<0.01
INR[c], median (IQR)		1.2 (1.1–1.4)	1.1 (1.0–1.3)	<0.01
Platelets (10^3/mm^3), median (IQR)		105 (69–155)	144 (100–202)	<0.01
Albumin (G/DL), median (IQR)		3.4 (2.9–3.8)	3.4 (2.95–3.8)	0.78

[a]Model End-Stage Liver Disease

[b]FIB-4 score – Fibrosis-4 (FIB-4) score

[c]INR – International Normalized Ratio

Table 4:

Liver Imaging Features

		Non-Black 805 patients	Black 390 patients	P value
Change in morphology – Lt hypertrophy or small liver		429 (56.5%)	155 (40.6%)	<0.01
Change in morphology – nodular liver		596 (78.5%)	190 (49.7%)	<0.01
Mild modularity		36 (4.7%)	40 (10.4%)	<0.01
Mention of cirrhosis in report		602 (79.3%)	184 (48.2%)	<0.01
Mild/early cirrhosis		31 (4.1%)	34 (8.9%)	0.001
Ascites		233 (30.7%)	66 (17.3%)	<0.01
Ascites	**Absent**	543 (67.6%)	311 (79.9%)	<0.01
	Mild (or suppressed under medication)	144 (17.9%)	41 (10.5%)	
	Moderate-severe (Refractory)	107 (13.3%)	31 (7.8%)	
Splenomegaly		425 (56.1%)	68 (17.8%)	<0.01
Varices		384 (50.7%)	75 (19.6%)	<0.01
Mention of Portal Hypertension in report		415 (54.7%)	78 (20.4%)	<0.01

Table 5:

Tumor imaging characteristics

		Non-Black N=805	Black N=390	P value
Size of largest tumor on imaging, median (IQR)		3.10 (2.10–5.10)	3.50 (2.20–6.20)	<0.01
Number of tumors on CT, Median (IQR)		1 (1–2)	1 (1–3)	0.03
Gross vascular invasion		147 (18.3%)	82 (21.2%)	<0.01
Metastasis		53 6.6%)	40 (10.3%)	0.03
AFP[a] (ng/ml), median (IQR)		46.4 (13.7–449.1)	32.7 (8.5–330.4)	<0.01
Bilateral tumors		107 (13.3%)	91 (23.2%)	<0.01
Within Milan criteria		475 (59.1%)	206 (53.0%)	0.043
BCLC[b] staging	**A**	424 (55.2%)	207 (53.2%)	<0.01
	B	113 (14.0%)	71 (18.3%)	
	C	146 (18.1%)	88 (22.6%)	
	D	102 (12.9%)	23 (5.9%)	

[a]AFP – Alpha Fetoprotein

[b]BCLC – Barcelona Clinic Liver Cancer

Table 6:

Tumor pathological characteristics

		Non-Black n=276	Black n=119	P value
Tumor size, median (IQR)		3.0 (2.1–4.4)	3.4 (2.2–5.1)	0.13
No. of tumors, median (IQR)		1 (1–2)	1 (1–2)	0.27
Presence of Dysplastic nodules/ satellite lesions		109 (39.5%)	60 (50.4%)	0.04
Microvascular invasion		151 (56.5%)	80 (67.2%)	0.04
Gross vascular invasion		34 (12.6%)	13 (11.2%)	0.70
Poor differentiation		56 (20.5%)	36 (30.3%)	0.03
Necrosis in tumor *		34 (21.5%)	12 (16.9%)	0.42
Pathological AJCC[a] TMN[b] stage	Stage 1 (a+b)	89 (32.2%)	24 (20.2%)	0.04
	Stage 2	147 (53.5%)	71 (59.7%)	
	Stage 3 (a+b)	36 (13.0%)	19 (16%)	
	Stage 4 (a+b)	4 (1.4%)	5 (4.2%)	

*In pathological reports of patients who did not receive prior treatment.

[a]AJCC – American Joint Committee on Cancer

[b]TNM – Tumor, Nodes, Metastases

Table 7:

Previous HBV [a] exposure: Liver function on diagnosis and tumor radiological characteristics

		All patients n=1006			Non-Black patients n=648			Black patients n=357			HBV exposed patients n=497		
		HBV− n=509	HBV+ n=497	p-value	HBV− n=363	HBV+ n=285	p-value	HBV− n=145	HBV+ n=212	p-value	Non black n=285	Black n=212	P value
Advancement of tumor													
Within Milan criteria		321 (63.2%)	278 (56%)	0.02	240 (66.3%)	172 (60.4%)	0.12	81 (55.5%)	106 (50.2%)	0.33	172 (60.4%)	106 (50.2%)	0.02
BCLC [b] score	**1**	296 (58.8%)	261 (52.8%)	0.25	218 (60.4%)	151 (53%)	0.25	78 (54.2%)	111 (52.6%)	0.89	78 (54.2%)	111 (52.6%)	0.02
	2	68 (13.5%)	85 (17.2%)		45 (12.5%)	45 (15.8%)		23 (16%)	41 (19.1%)		23 (16%)	41 (19.1%)	
	3	86 (17%)	89 (18%)		54 (15%)	45 (15.8%)		32 (22.2%)	45 (21.1%)		32 (22.2%)	45 (21.1%)	
	4	55 (10.9%)	59 (11.9%)		44 (12.2%)	44 (15.4%)		11 (7.6%)	15 (7.2%)		11 (7.6%)	15 (7.2%)	
Tumor Size (cm)		2.9 (2.1–4.6)	3.4 (2.1–5.4)	0.04	2.8 (2.4.5)	3.1 (2.1–4.8)	0.10	3 (2.1–4.9)	3.5 (2.3–6.6)	0.05	3 (2.1–4.9)	3.5 (2.3–6.6)	0.01
Tumor size > 2.5 cm		283 (55.6%)	317 (63.8%)	0.03	197 (54.3%)	175 (61.4%)	0.19	86 (58.9%)	142 (67%)	0.29	175 (61.4%)	142 (67%)	0.134
Number Of tumors		1 (1–2)	1 (1–3)	0.01	1 (1–2)	1 (1–2)	0.56	1 (1–2)	2 (1–4)	0.04	1 (1–2)	2 (1–4)	<0.01
Gross vascular invasion		86 (17%)	89 (17.9%)	0.70	57 (15.8%)	45 (15.8%)	1	29 (20.1%)	44 (20.9%)	0.87	45 (15.8%)	44 (20.9%)	0.15
metastasis		35 (7.1%)	37 (7.8%)	0.67	19 (5.4%)	18 (6.6%)	0.52	16 (11.1%)	19 (9.3%)	0.57	18 (6.6%)	19 (9.3%)	0.29
Laboratory:													
age		60 (55–67)	60 (55–65)	0.17	60 (54–66)	59 (54–64)	0.24	62 (56–68)	61 (56–65)	0.08	59 (54–64)	61 (56–65)	0.01
insurance		198 (38.9%)	157 (31.6%)	<0.01	156 (43%)	108 (37.9%)	0.19	42 (28.8%)	49 (23.1%)	0.407	108 (37.9%)	49 (23.1%)	<0.01
INR [c]		1.2 (1.1–1.4)	1.2 (1.1–1.4)	0.96	1.2 (1–1.4)	1.2 (1–1.4)	0.12	1.1 (1–1.3)	1.1 (1–1.3)	0.37	1.2 (1–1.4)	1.1 (1–1.3)	<0.01
Platelets (10^3/mm^3)		114 (73–166)	116 (76–168)	0.69	101 (68–150)	95 (68–140)	0.29	139 (111–195)	145 (92–203)	0.77	95 (68–140)	145 (92–203)	<0.01
Bilirubin (mg/dL)		1.1 (0.7–2)	1.2 (0.7–2)	0.44	1.1 (0.7–2.3)	1.3 (0.8–2.2)	0.12	1 (0.6–1.5)	0.9 (0.6–2)	0.96	1.3 (0.8–2.2)	0.9 (0.6–2)	<0.01
Albumin (G/dL)		3.4 (2.9–3.8)	3.3 (2.8–3.8)	0.44	3.4 (2.9–3.9)	3.3 (2.7–3.8)	0.11	3.3 (2.8–3.8)	3.4 (2.9–3.8)	0.41	3.3 (2.7–3.8)	3.4 (2.9–3.8)	0.15
FIB-4 [d] score		6.1 (3.6–9.9)	6 (3.4–10.2)	0.52	6.5 (3.9–10.6)	6.9 (4.4–11)	0.41	5.3 (3.1–7.6)	4.5 (2.8–8.3)	0.39	6.9 (4.4–11)	4.5 (2.8–8.3)	<0.01
MELD [e] score		10 (7–15)	10 (7–16)	0.17	10 (7–16)	11 (8–16)	0.15	9 (7–14)	9 (8–16)	0.59	11 (8–16)	9 (8–16)	0.14
CHILD-PUGH score	**A**	310 (61%)	289 (58.1%)	0.59	217 (59.8%)	145 (50.9%)	0.07	93 (64.1%)	144 (67.9%)	0.74	145 (50.9%	144 (67.9%	<0.01

		All patients n=1006			Non-Black patients n=648			Black patients n=357			HBV exposed patients n=497		
		HBV− n=509	HBV+ n=497	p-value	HBV− n=363	HBV+ n=285	p-value	HBV− n=145	HBV+ n=212	p-value	Non black n=285	Black n=212	P value
	B	141 (27.8%)	44 (29%)		101 (27.8%)	93 (32.6%)		40 (27.6%)	51 (24.1%)		93 (32.6%)	51 (24.1%)	
	C	57 (11.2%)	64 (12.9%)		45 (6.9%)	47 (7.3%)		107 (13.7%)	17 (8%)		47 (7.3%)	17 (8%)	

Categorical variables reported as total (%), continuous variables reported as median (IQR)

[a] HBV – Hepatitis B virus

[b] BCLC – Barcelona Clinic Liver Cancer

[c] INR – International Normalized Ratio

[d] FIB-4 score – fibrosis-4 score

[e] MELD = Model End-Stage Liver Disease

Table 8:

HIV [a] co-infection: Liver function on diagnosis and tumor radiological characteristics

		All patients			Non-Black patients			Black patients			HIV positive patients		
		HIV− 999	HIV+ 196	p-value	HIV− n=699	HIV+ N=106	p-value	HIV− n=300	HIV+ n=90	p-value	Non-Black 106	black 90	P-value
Advancement of tumor													
Within Milan criteria		553 (55.4%)	133 (67.9%)	<0.01	401 (57.2%)	79 (74.5%)	<0.01	152 (50.7%)	54 (60%)	0.12	79 (74.5%)	54 (60%)	0.03
BCLC [b] score	**1**	521 (52.1%)	126 (64.3%)	<0.01	371 (53%)	70 (66%)	<0.01	150 (50%)	56 (62.2%)	0.03	70 (66%)	56 (62.2%)	<0.01
	2	162 (16.2%)	24 (12.2%)		108 (15.5%)	6 (5.7%)		54 (17.9%)	18 (20%)		6 (5.7%)	18 (20%)	
	3	198 (19.9%)	38 (19.4%)		124 (17.8%)	15 (16.7%)		74 (24.7%)	23 (21.7%)		23 (21.7%)	15 (16.7%)	
	4	118 (11.7%)	8 (6.3%)		96 (13.8%)	7 (6.6%)		22 (7.4%)	1 (4.3%)		7 (6.6%)	1 (4.3%)	
Tumor Size (cm)		3.3 (2.2–5.4)	2.9 (2–4.5)	0.02	3.2 (2.1–5.1)	2.7 (1.8–4.3)	0.02	3.5 (2.3–6.7)	3.1 (2.1–4.9)	0.13	2.7 (1.8–4.3)	3.1 (2.1–4.9)	0.08
Tumor >2.5 cm		629 (62.9%)	109 (55.6%)	0.025	429 (61.3%)	54 (50.9%)	0.03	200 (67.3%)	55 (61.1%)	0.18	54 (50.9%)	55 (61.1%)	0.18
Number of tumors		1 (1–3)	1 (1–2)		1 (1–2)	1 (1–1)	<0.01	1 (1–3)	1 (1–2)	0.09	1 (1–1)	1 (1–2)	0.01
Gross vascular invasion		195 (19.5%)	36 (18.4%)	0.75	126 (18%)	23 (21.7%)	0.32	69 (23%)	13 (14.4%)	0.09	23 (21.7)	13 (14.4%)	0.194
metastasis		82 (8.2%)	10 (5.1%)	0.124	48 (6.9%)	4 (3.8%)	0.22	34 (11.9%)	6 (6.7%)	0.16	4 (3.8%)	6 (6.7%)	0.393
Laboratory													
Age		60 (55–66)	60 (55–64)	0.25	59 (54–66)	60 (54–64)	0.55	62 (56–66)	60 (55–65)	0.07	60 (54–64)	60 (55–65)	0.29
Commercial insurance		366 (36.6%)	61 (31%)	0.14	286 (40%)	40 (37.7%)	0.53	87 (29%)	21 (23%)	0.29	40 (37.7%)	21 (23%)	0.04
INR [c]		1.2 (1.1–1.4)	1.1 (1–1.3)	<0.01	1.2 (1.1–1.4)	1.1 (1.1–1.3)	0.02	1.1 (1–1.3)	1 (1–1.2)	0.34	1.1 (1.1–1.3)	1.1 (1–1.2)	0.09
Platelets (10^3/ mm^3)		113 (74–168)	136 (90–185)	<0.01	101 (68–154)	123 (80–170)	<0.01	136 (96–198)	149 (106–203)	0.31	123 (80–170)	149 (106–203)	<0.01
Bilirubin (mg/dL)		1.1 (0.7–2.1)	0.8 (0.6–1.4)	<0.01	1.2 (0.8–2.2)	0.9 (0.6–1.6)	<0.01	0.9 (0.6–1.6)	0.8 (0.5–1.3)	0.02	0.9 (0.6–1.6)	0.8 (0.5–1.3)	0.15
Albumin (G/DL)		3.4 (2.9–3.8)	3.5 (3–4)	0.02	3.3 (2.9–3.8)	3.6 (2.9–4.1)	0.01	3.4 (2.9–3.9)	3.4 (3–3.9)	0.64	3.6 (2.9–4.1)	3.4 (3–3.9)	0.10
FIB-4 [d] score		6.2 (3.7–10)	4.7 (3.1–7.4)	<0.01	6.7 (4.1–10.6)	5.5 (3.4–8.9)	0.02	4.9 (3–8.2)	3.6 (2.6–6.7)	0.01	5.5 (3.4–8.9)	3.6 (2.6–6.7)	<0.01
MELD [e] score		10 (7–16)	8 (7–14)	<0.01	10 (7–16)	9 (7–14)	<0.01	9 (7–14)	8 (7–14)	0.08	9 (7–14)	8 (7–14)	0.90
CHILD PUGH score	**A**	599 (59.9%)	141 (71.9%)	<0.01	401 (57.3%)	71 (67%)	0.04	198 (66.7%)	70 (77.8%)	0.04	71 (67%)	70 (77.8%)	0.09

		All patients			Non-Black patients			Black patients			HIV positive patients		
		HIV− 999	HIV+ 196	p-value	HIV− n=699	HIV+ N=106	p-value	HIV− n=300	HIV+ n=90	p-value	Non-Black 106	black 90	P-value
	B	279 (27.9%)	46 (23.4%)		202 (28.8%)	27 (25.5%)		80 (26.6%)	19 (21.1%)		27 (25.5%)	19 (21.1%)	
	C	121 (12.1%)	9 (0.8%)		96 (13.8%)	8 (7.5%)		22 (7.3%)	1 (1.1%)		8 (7.5%)	1 (1.1%)	

** Categorical variables reported as total (%), continuous variables reported as median (IQR)

[a] HIV – Human Immunodeficiency Virus

[b] BCLC – Barcelona Clinic Liver Cancer

[c] INR – International Normalized Ratio

[d] FIB-4 score – fibrosis-4 score

[e] MELD = Model End-Stage Liver Disease

Table 9:

HCV[a] Mono-infection: Liver function on diagnosis and tumor radiological and pathological characteristics (excluding: HBV[b] exposure, HIV[c]+, no information about HBV status)

	Non-Black n=314	Black n=117	p-value
liver Function on Diagnosis			
Age, median (IQR)	59 (54–66)	53 (57–68)	<0.01
insurance	137 (43.6%)	32 (27.3%)	<0.01
INR [d], median (IQR)	1.2 (1.1–1.4)	1.1 (1–1.3)	0.02
Platelets (10^3/mm^3), median (IQR)	99 (67–144)	135 (100–196)	<0.01
Total bilirubin (mg/dL), median (IQR)	1.2 (0.7–2.3)	1.1 (0.6–1.7)	0.03
Albumin (G/DL), median (IQR)	3.3 (2.9–3.8)	3.4 (2.8–3.8)	0.93
MELD[e] SCORE, median (IQR)	6.6 (4.1–10.6)	5.6 (3.2–8.1)	0.01
CHILD PUGH score			0.56
A	182 (58%)	73 (62.4%)	
B	89 (28.3%)	32 (27.4%)	
C	43 (13.7%)	12 (10.2%)	
FIB-4[f] score, median (IQR)	6.6 (4.1–10.6)	5.6 (3.2–8.1)	0.01
FIB-4 score < 3.25	57 (18.2%)	31 (26.5%)	0.05
tumor imaging characteristic			
Within MILAN criteria	195 (62.3%)	61 (52.1%)	0.05
BCLC [g] staging			0.06
1	178 (57.1%)	58 (50.4%)	
2	43 (13.8%)	16 (13.9%)	
3	48 (15.4%)	30 (26.1%)	
4	43 (13.8%)	11 (9.6%)	
Tumor Size, median (IQR)	2.9 (2.1–4.8)	3.5 (2.1–5.8)	0.19
Tumor size>2.5 cm	180 (59.8%)	69 (63.9%)	0.46
Number of tumors, median (IQR)	1 (1–2)	1 (1–2)	0.56

	Non-Black n=314	Black n=117	p-value
Gross vascular invasion	51 (16.3%)	28 (23.9%)	0.07
metastasis	20 (6.6%)	14 (12.2%)	0.05
Pathological report (resected/transplanted patients)			
	Non black 129 patients	Black 33 patients	
Microvascular invasion	68 (52.7%)	26 (78.8%)	<0.01
Nodules/satellite lesions	53 (41.7%)	18 (58.1%)	0.10
Poor differentiation	25 (19.3%)	8 (24.2%)	0.62
Pathological AJCC [h] **TMN** [i] **stage 1**	27 (16.7%)	1 (3%)	0.01

[a] HCV – hepatitis C virus

[b] HBV – Hepatitis B virus

[c] HIV – Human Immunodeficiency Virus

[d] INR – International Normalized Ratio

[e] MELD = Model End-Stage Liver Disease

[f] FIB-4 score – fibrosis-4 score

[g] BCLC – Barcelona Clinic Liver Cancer

[h] AJCC – American Joint Committee on Cancer

[i] TMN – Tumor, Nodes, Metastasis.