Original Article

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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BACKGROUND: 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. The objective of this study was to clarify factors contributing to this disparity by analyzing liver and tumor characteristics in patients with HCC who have a history of hepatitis C virus (HCV) infection. **METHODS:** Records of patients with HCV and HCC at the authors' institution from 2003 to 2018 were retrospectively reviewed. Race and ethnicity were self-identified. Imaging, laboratory, and pathologic features were compared between Black and non-Black cohorts. **RESULTS:** Among 1195 individuals with HCC, 390 identified as Black. At the time of HCC diagnosis, Black patients had better liver function, as measured by Child-Pugh score, Model of End-Stage Liver Disease score, histology of nontumor tissue, and fibrosis-4 (FIB-4) score (all $P < .05$). 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%; $P < .05$), larger tumors (median [interquartile range]: 3.5 cm [2.2-6.2 cm] vs 3.1 cm [2.1-5.1 cm]; $P < .01$), more multiple tumors (median, [interquartile range]: 1 tumor [1-3 tumors] vs 1 tumor [1-2 tumors]; $P = .03$), more poorly differentiated tumors (30.3% vs 20.5%; $P < .05$), and more microvascular invasion (67.2% vs 56.5%; $P < .05$). **CONCLUSIONS:** 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 that stress HCC surveillance for cirrhotic patients with HCV may need to be revised to be more inclusive for Black patients. In addition, tumors in Black patients carry worse prognostic features, and molecular studies are needed to characterize their biologic properties. ***Cancer* 2021;127:1395-1406**. © *2021 American Cancer Society*.

KEYWORDS: Black race, cirrhosis, disparities, hepatitis C virus, hepatocellular carcinoma, surveillance.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the second leading cause of site-specific, cancer-related death around the world.[1] According to the National Cancer Institute's Surveillance, Epidemiology, and End Results 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.[2] In 2012, age-adjusted HCC incidence rates were 6.7 per 100,000.[3] In the latest Annual Report on the Status of Cancer in the United States 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 United States: during 2005 through 2007, the HCC incidence in the Black population was 1.5-fold higher than that in the general population.[6] Hepatitis C virus (HCV) infection is the leading risk factor for liver cancer in the United States[7,8] and also affects communities disproportionately: the estimated prevalence of HCV in the general population is 1.67% (95% CI, 1.53%-1.90%),[9] compared with 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 those with extrahepatic metastases.[11] Many patients are diagnosed with advanced HCC and receive only palliative treatment; however, early stage HCC can be cured with surgery. The 5-year survival rate for patients who underwent surgery for early stage HCC was 50%, underscoring the importance of early detection at a potentially curative stage.[12]

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Black patients with HCC have the lowest overall survival of any racial or 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 patients of other racial or 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,[20,21] the European Association for the Study of Liver Disease,[22] and the Asian Pacific Association for the Study of Liver Disease[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 (a fibrosis score of F3 according to the French METAVIR Cooperative Study Group scoring system) are also at elevated risk for developing HCC.[25] Accordingly, the European Association for the Study of Liver Disease recommends HCC surveillance for patients with bridging fibrosis in addition to patients with definite cirrhosis.[22] The Fibrosis-4 Index for Liver Fibrosis (FIB-4) score is a noninvasive alternative to biopsy: an FIB-4 score >3.25 correlates with advanced fibrosis and cirrhosis[26] and has a positive predictive value of 82% with 98% specificity 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 patients than in 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 (hazard ratio, 0.58; 95 % CI, 0.55-0.60).[28] Consistent with this finding, a small study from our group demonstrated that Black patients had 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. Those authors observed 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, our objective was to compare liver function and the presence of cirrhosis at the time of HCC diagnosis between Black patients and non-Black patients with a history of HCV infection. Our secondary objective was to investigate whether HCC in Black patients with a history of HCV is associated with a more aggressive phenotype, as a potential biologic 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 *International Classification of Diseases and Related Health Problems, Ninth Revision* 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 1 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.

Clinicopathologic Variables

Demographic, clinical, and socioeconomic factors, including age, sex, body mass index, and type of insurance, were collected. Government-insured patients were defined as those with Medicaid and those with Medicare and no supplemental insurance. Commercially insured patients were defined as those with nongovernment-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 (ongoing) 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-HBcAb–positive). HBV exposure was defined as the presence of at least 1 of the 2 following serum factors: anti-HBcAb, HBsAg, and/or HBV DNA. HIV infection was defined by the presence of HIV RNA and/or anti-HIV antibodies in serum. Any history of HCV treatment (interferon, ribavirin, interferon plus ribavirin, direct-acting antivirals, or interferon/ribavirin plus direct-acting antivirals) was recorded. A sustained virologic response was defined as aviremia 24 weeks after the completion of HCV treatment.

Laboratory Variables

Laboratory data included platelet counts, albumin and total bilirubin levels, the international normalized ratio, and α-fetoprotein (AFP) levels. Values from the date closest to HCC diagnosis were used. Liver function and cirrhosis were determined using the Model of End-Stage Liver Disease (MELD) the score, Child-Pugh classification, and FIB-4 index score, a validated noninvasive tool to estimate hepatic fibrosis stage. The FIB-4 is calculated as follows: age (years) × aspartate aminotransferase (U/L)/platelets (10^9/L) + alanine aminotransferase (U/L).

Imaging Variables

Imaging data at the time of HCC diagnosis were collected. Imaging modalities included abdominal contrast-enhanced computerized tomography and magnetic resonance imaging. 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), and the presence of ascites, varices, or splenomegaly. Mentions of *cirrhosis* and *portal hypertension* in computed tomography/magnetic resonance imaging reports were recorded.

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

Pathologic Variables

For patients who underwent resection or transplantation and had a pathology report, we recorded the METAVIR scores of the nontumor liver parenchyma.[31,32] The METAVIR system classifies the stage of fibrosis on a 5-point scale, from F0 (no fibrosis) to F4 (cirrhosis), and classifies histologic activity on a 4-point scale, from A0 (no activity) to A3 (severe activity). Data on tumor characteristics also were collected, including tumor size, number, differentiation, necrosis, the presence of dysplastic nodules and satellite lesions, microvascular invasion, gross vascular invasion, tumor necrosis, tumor margins resection, and staging according to the tumor, lymph node, metastasis (TNM) classification (American Joint Committee on Cancer *AJCC Cancer Staging Manual*, eighth edition).

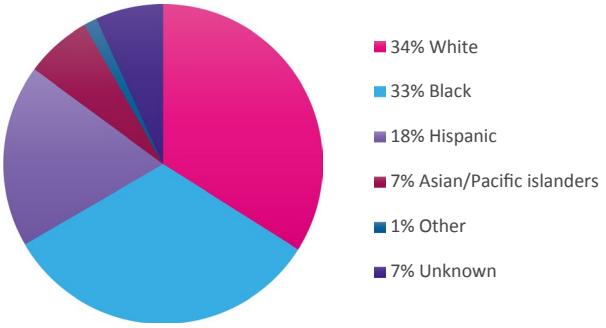

Figure 1. The distribution of patients with chronic hepatitis C virus (HCV) and hepatocellular carcinoma (HCC) is illustrated according to racial/ethnic group. NS indicates nonsignificant.

Statistical Analysis

Data were analyzed with the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corporation) using a significance level of .05. Chi-square or Fisher 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 was compared using the log-rank test.

RESULTS

Study Group

Between 2003 and 2018, 1195 patients who had HCC and a history of HCV infection were 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) (Fig. 1, Table 1). Most patients were men, and the distribution of sex did not differ

TABLE 1. Patient Characteristics

Characteristic	No. of Patients (%)		P
	Non-Black, N = 805	Black, N = 390	
Sex			
Men	621 (77.1)	288 (73.6)	NS
Women	184 (22.9)	102 (26.2)	
Age: Median [IQR], y	59 [54-66]	62 [57-67]	<.01
BMI: Median [IQR], kg/m^2	26.91 [24.02-30.30]	26.30 [22.65-29.59]	<.01
Commercial insurance	326 (40.4)	101 (25.9)	<.01
Chronic HBV co-infection	29 (3.6)	23 (5.9)	.07
Previous HBV exposure	285 (49.3)	212 (59.3)	<.01
HIV co-infection	106 (13.2)	90 (23.3)	<.01
HCV treatment SVR	55 (6.7)	27 (7.0)	.954

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; NS, nonsignificant; SVR, sustained virologic response.

between Black patients and other patients. Black patients were slightly older at the time of HCC diagnosis (median age, 62 vs 59 years; $P < .01$), had slightly lower body mass index (26.3 vs 26.9 kg/m^2; $P < .01$), and were less likely to have commercial insurance (25.9% vs 40%; $P < .01$). In total, 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%; $P < .01$; HBV: 49.3% vs 59.3%; $P < .01$). At the time of HCC diagnosis, 81 patients had been cured of HCV, with similar proportions in the Black and non-Black cohorts. Among 395 patients who underwent surgery and had an available pathology report, 238 patients underwent resection, and 157 underwent liver transplantation; the distribution according to surgical procedure type was similar in the Black and non-Black cohorts (Fig. 2).

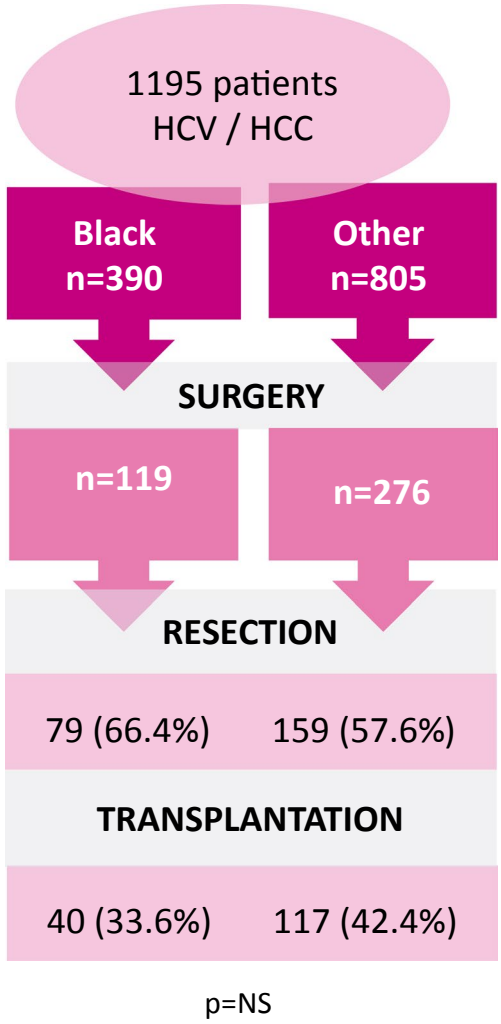

Figure 2. The distribution of surgical treatment and type of surgery is illustrated in patients with hepatocellular carcinoma according to racial/ethnic group.

Liver Function, Fibrosis Stage, and Child-Pugh 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 2, at the time of 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; $P < .01$), a lower median international normalized ratio (1.1 vs 1.2; $P < .01$), and a lower median bilirubin level (0.90 vs 1.2 mg/dL; $P < .01$). Black patients were more likely to have Child-Pugh class A cirrhosis than the remainder of the cohort (69.4% vs 58.5%; $P < .01$) and were 2-fold less likely to have Child-Pugh C cirrhosis (5.9% vs 12.9%; $P < .01$). Black patients' median MELD score was lower (9.0 vs 10; $P < .01$), as was their median FIB-4 score (4.66 vs 6.54; $P < .01$), which is particularly notable because the median age of Black individuals was older; all other factors being equal, the FIB-4 score increases with the age of the patient. Thirty-one percent of Black patients had an FIB-4 score <3.25 at the time of HCC diagnosis. Consistent with these findings, among 339 patients with histopathologic data, Black patients had less advanced liver disease in nontumor tissue: 35% did not have cirrhosis (defined as a METAVIR score of F4), and 20% had METAVIR

TABLE 2. Liver Function on Diagnosis: Laboratory and Histology

Variable	No. of Patients (%)		*P*
	Non-Black, N = 805	Black, N = 390	
Child-Pugh score			
A	466 (58.5)	270 (69.4)	<.01
B	231 (28.9)	96 (24.7)	
C	103 (12.9)	23 (5.9)	
MELD score: Median [IQR]	10 [7-16]	9 [7-14]	.02
FIB-4 score: Median [IQR]	6.54 [3.99-10.53]	4.66 [2.94-7.52]	<.01
FIB-4 score <3.25	143 (17.8)	122 (31.1)	<.01
Total bilirubin: Median [IQR], mg/dL	1.20 [0.7-2.2]	0.90 [0.60-1.50]	<.01
INR: Median [IQR]	1.2 [1.1-1.4]	1.1 [1.0-1.3]	<.01
Platelets: Median [IQR], 10^3/mm^3	105 [69-155]	144 [100-202]	<.01
Albumin: Median [IQR], g/dL	3.4 [2.9-3.8]	3.4 [2.95-3.8]	.78

Abbreviations: FIB-4 score, Fibrosis-4 Index for Liver Fibrosis score; INR, international normalized ratio; IQR, interquartile range; MELD, Model End-Stage Liver Disease.

TABLE 3. Pathologic Liver Disease Staging and Grading

Variable	No. of Patients (%)		*P*
	Non-Black, N = 233	Black, N = 106	
Pathologic inflammatory activity grading, N = 339			
1	33 (14.2)	20 (18.9)	.230
2	169 (72.5)	79 (74.5)	
3	29 (12.4)	7 (6.6)	
4	2 (0.9)	0 (0.0)	
Pathologic liver fibrosis staging, N = 339			
1	4 (1.7)	2 (1.9)	<.01
2	17 (7.3)	21 (19.6)	
3	25 (10.7)	15 (14.0)	
4	187 (80.3)	68 (63.6)	

scores from F0 to F2. The grade of inflammation was similar in both groups (Table 3).

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%; $P < .01$) and less likely to have a liver with altered morphology, as indicated by hypertrophy of the left lobe or small overall liver size ($P < .01$). Portal hypertension was reported in 20% of Black individuals versus 55% in non-Black individuals ($P < .01$). Black patients were less likely to have ascites, varices, and splenomegaly ($P < .05$ for all). Only 50% of imaging reports from Black patients mentioned *cirrhosis* versus 79% of non-Black patients, and mild cirrhosis was noted more frequently (8.9% vs 4.1%; $P < .01$).

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 ($P = .04$). There was a statistically significant difference in Barcelona Clinic Liver Cancer staging between Black patients and the remainder of the cohort ($P < .01$). 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%; $P < .05$) and to show microvascular invasion (67.2% vs 56.5%; $P = .04$) (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%; $P < .05$). The groups were comparable in the prevalence of tumor necrosis.

The Impact of HBV and HIV

Patients with HBV exposure (ie, positive for 1 or more HBV proteins and/or DNA and/or HBc antibodies) 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 greatest dimension, and tumors were more likely to be multifocal. A subgroup analysis was performed to assess whether some of the unfavorable characteristics of HCC in Black patients were because of their higher prevalence of HBV exposure and the unfavorable characteristics of HBV-associated HCC. A comparison between Black patients and non-Black patients who had HBV exposure demonstrated that Black patients had less liver fibrosis at the time of HCC diagnosis (median FIB-4 score [interquartile range (IQR)], 4.5 [2.8-8.3] vs 6.9 [4.4-11]; $P < .01$) and worse tumor characteristics, defined as larger tumors, multiple tumors, and a smaller percentage within Milan criteria (Table 7). Because all patients in this subanalysis 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

TABLE 4. Liver Imaging Features

Feature	No. of Patients (%)		*P*
	Non-Black, N = 805	Black, N = 390	
Change in morphology, Left lobe hypertrophy or small liver	429 (56.5)	155 (40.6)	<.01
Change in morphology, nodular liver	596 (78.5)	190 (49.7)	<.01
Mild modularity	36 (4.7)	40 (10.4)	<.01
Mention of cirrhosis in report	602 (79.3)	184 (48.2)	<.01
Mild/early cirrhosis	31 (4.1)	34 (8.9)	.001
Ascites	233 (30.7)	66 (17.3)	<.01
Absent	543 (67.6)	311 (79.9)	<.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)	<.01
Varices	384 (50.7)	75 (19.6)	<.01
Mention of portal hypertension in report	415 (54.7)	78 (20.4)	<.01

TABLE 5. Tumor Imaging Characteristics

Characteristic	No. of Patients (%)		*P*
	Non-Black, N = 805	Black, N = 390	
Size of largest tumor on imaging: Median [IQR], cm	3.10 [2.10-5.10]	3.50 [2.20-6.20]	<.01
No. of tumors on CT: Median [IQR]	1 [1-2]	1 [1-3]	.03
Gross vascular invasion147 (18.3)	82 (21.2)	<.01	
Metastasis	53 (6.6)	40 (10.3)	.03
AFP: Median [IQR], ng/mL	46.4 [13.7-449.1]	32.7 [8.5-330.4]	<.01
Bilateral tumors	107 (13.3)	91 (23.2)	<.01
Within Milan criteria	475 (59.1)	206 (53.0)	.043
BCLC staging			
A	424 (55.2)	207 (53.2)	<.01
B	113 (14.0)	71 (18.3)	
C	146 (18.1)	88 (22.6)	
D	102 (12.9)	23 (5.9)	

Abbreviations: AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CT, computed tomography; IQR, interquartile range.

TABLE 6. Tumor Pathologic Characteristics

Characteristic	No. of Patients (%)		*P*
	Non-Black, n = 276	Black, n = 119	
Tumor size: Median [IQR], cm	3.0 [2.1-4.4]	3.4 [2.2-5.1]	.13
No. of tumors: Median [IQR]	1 [1-2]	1 [1-2]	.27
Presence of dysplastic nodules/satellite lesions	109 (39.5)	60 (50.4)	.04
Microvascular invasion	151 (56.5)	80 (67.2)	.04
Gross vascular invasion	34 (12.6)	13 (11.2)	.70
Poor differentiation	56 (20.5)	36 (30.3)	.03
Necrosis in tumor[a]	34 (21.5)	12 (16.9)	.42
Pathologic AJCC TNM classification			
Stage IA + IB	89 (32.2)	24 (20.2)	.04
Stage II	147 (53.5)	71 (59.7)	
Stage IIIA + IIIB	36 (13.0)	19 (16)	
Stage IVA + IVB	4 (1.4)	5 (4.2)	

Abbreviations: AJCC TNM, American Joint Committee on Cancer tumor, lymph node, metastasis classification; IQR, interquartile range
[a]Data on the presence of necrosis were obtained from pathologic reports in patients who did not receive prior treatment.

in HIV-positive non-Black patients than in HIV-positive Black patients (Table 8).

We performed a subanalysis 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 2 viruses (Table 9). In this subanalysis, 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 they were less likely to be within Milan criteria, less likely to have TNM stage I disease, and more likely to have extrahepatic metastases and microvascular invasion (all $P \leq .05$).

Long-Term Survival

Survival analysis was performed on 780 patients who had at least 5 years of follow-up data. Black patients had a shorter overall median survival (18 months [IQR, 6-67 months] vs 30 months [IQR, 9-90 months]; $P < .01$). The 5-year survival rate was 21% in Black patients and 28.4% in the remainder of the cohort ($P = .02$); 1-year survival did not differ between groups (Fig. 3).

DISCUSSION

This study uncovered 2 striking features of HCC in Black patients with a history of HCV infection, indicating 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

TABLE 7. Previous Hepatitis B Virus Exposure: Liver Function on Diagnosis and Tumor Radiologic Characteristics[a]

	All Patients, N = 1006			Non-Black Patients, n = 648			Black Patients, n = 357			HBV-Exposed Patients, n = 497		
	No. (%)			No. (%)			No. (%)			No. (%)		
Characteristic	HBV-Negative, n = 509	HBV-Positive, n = 497	*P*	HBV-Negative, n = 363	HBV-Positive, n = 285	*P*	HBV-Negative, n = 145	HBV-Positive, n =212	*P*	Non-Black, n = 285	Black, n = 212	*P*
Advancement of tumor												
Within Milan criteria	321 (63.2)	278 (56.0)	.02	240 (66.3)	172 (60.4)	.12	81 (55.5)	106 (50.2)	.33	172 (60.4)	106 (50.2)	.02
BCLC score												
A	296 (58.8)	261 (52.8)	.25	218 (60.4)	151 (53)	.25	78 (54.2)	111 (52.6)	.89	78 (54.2)	111 (52.6)	.02
B	68 (13.5)	85 (17.2)		45 (12.5)	45 (15.8)		23 (16.0)	41 (19.1)		23 (16.0)	41 (19.1)	
C	86 (17.0)	89 (18)		54 (15)	45 (15.8)		32 (22.2)	45 (21.1)		32 (22.2)	45 (21.1)	
D	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: Median [IQR], cm	2.9 [2.1-4.6]	3.4 [2.1-5.4]	.04	2.8 [2.4-5.0]	3.1 [2.1-4.8]	.10	3.0 [2.1-4.9]	3.5 [2.3-6.6]	.05	3.0 [2.1-4.9]	3.5 [2.3-6.6]	.01
Tumor size >2.5 cm	283 (55.6)	317 (63.8)	.03	197 (54.3)	175 (61.4)	.19	86 (58.9)	142 (67.0)	.29	175 (61.4)	142 (67)	.134
No. of tumors [IQR]	1 [1-2]	1 [1-3]	.01	1 [1-2]	1 [1-2]	.56	1 [1-2]	2 [1-4]	.04	1 [1-2]	2 [1-4]	<.01
Gross vascular invasion	86 (17)	89 (17.9)	.70	57 (15.8)	45 (15.8)	1.00	29 (20.1)	44 (20.9)	.87	45 (15.8)	44 (20.9)	.15
Metastasis	35 (7.1)	37 (7.8)	.67	19 (5.4)	18 (6.6)	.52	16 (11.1)	19 (9.3)	.57	18 (6.6)	19 (9.3)	.29
Patient and laboratory variables												
Age: Median [IQR], y	60 [55-67]	60 [55-65]	.17	60 [54-66]	59 [54-64]	.24	62 [56-68]	61 [56-65]	.08	59 [54-64]	61 [56-65]	.01
Insurance	198 (38.9)	157 (31.6)	<.01	156 (43.0)	108 (37.9)	.19	42 (28.8)	49 (23.1)	.407	108 (37.9)	49 (23.1)	<.01
INR	1.2 [1.1-1.4]	1.2 [1.1-1.4]	.96	1.2 [1.0-1.4]	1.2 [1.0-1.4]	.12	1.1 [1.0-1.3]	1.1 [1.0-1.3]	.37	1.2 [1.0-1.4]	1.1 [1.0-1.3]	<.01
Platelets: Median [IQR], $10^3/mm^3$	114 [73-166]	116 [76-168]	.69	101 [68-150]	95 [68-140]	.29	139 [111-195]	145 [92-203]	.77	95 [68-140]	145 [92-203]	<.01
Bilirubin: Median [IQR], mg/dL	1.1 [0.7-2.0]	1.2 [0.7-2.0]	.44	1.1 [0.7-2.3]	1.3 [0.8-2.2]	.12	1.0 [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: Median [IQR], g/dL	3.4 [2.9-3.8]	3.3 [2.8-3.8]	.44	3.4 [2.9-3.9]	3.3 [2.7-3.8]	.11	3.3 [2.8-3.8]	3.4 [2.9-3.8]	.41	3.3 [2.7-3.8]	3.4 [2.9-3.8]	.15
FIB-4 score: Median [IQR]	6.1 [3.6-9.9]	6.0 [3.4-10.2]	.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]	.39	6.9 [4.4-11.0]	4.5 [2.8-8.3]	<.01
MELD score: Median [IQR], Child-Pugh score	10 [7-15]	10 [7-16]	.17	10 [7-16]	11 [8-16]	.15	9 [7-14]	9 [8-16]	.59	11 [8-16]	9 [8-16]	.14
A	310 (61.0)	289 (58.1)	.59	217 (59.8)	145 (50.9)	.07	93 (64.1)	144 (67.9)	.74	145 (50.9)	144 (67.9)	<.01
B	141 (27.8)	44 (29.0)		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 (8.0)		47 (7.3)	17 (8.0)	

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; FIB-4 score, Fibrosis-4 Index for Liver Fibrosis score; HBV, hepatitis B virus; INR, international normalized ratio; IQR, interquartile range; MELD, Model End-Stage Liver Disease.

[a]Categorical variables are reported as total numbers (%), and continuous variables are reported as medians (IQRs).

TABLE 8. Human Immunodeficiency Virus Co-Infection: Liver Function on Diagnosis and Tumor Radiologic Characteristics[a]

	All Patients			Non-Black Patients			Black Patients			HIV-Positive Patients		
	No. (%)			No. (%)			No. (%)			No. (%)		
Characteristic	HIV-Negative, N = 999	HIV-Positive, N = 196	*P*	HIV-Negative, n = 699	HIV-Positive, n = 106	*P*	HIV-Negative, n = 300	HIV-Positive, n = 90	*P*	Non-Black, n = 106	Black, n = 90	*P*
Advancement of tumor												
Within Milan criteria	553 (55.4)	133 (67.9)	<.01	401 (57.2)	79 (74.5)	<.01	152 (50.7)	54 (60.0)	.12	79 (74.5)	54 (60.0)	.03
BCLC score												
A	521 (52.1)	126 (64.3)	<.01	371 (53)	70 (66)	<.01	150 (50)	56 (62.2)	.03	70 (66)	56 (62.2)	<.01
B	162 (16.2)	24 (12.2)		108 (15.5)	6 (5.7)		54 (17.9)	18 (20)		6 (5.7)	18 (20.0)	
C	198 (19.9)	38 (19.4)		124 (17.8)	15 (16.7)		74 (24.7)	23 (21.7)		23 (21.7)	15 (16.7)	
D	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: Median [IQR], cm	3.3 [2.2-5.4]	2.9 [2.0-4.5]	.02	3.2 [2.1-5.1]	2.7 [1.8-4.3]	.02	3.5 [2.3-6.7]	3.1 [2.1-4.9]	.13	2.7 [1.8-4.3]	3.1 [2.1-4.9]	.08
Tumor >2.5 cm	629 (62.9)	109 (55.6)	.025	429 (61.3)	54 (50.9)	.03	200 (67.3)	55 (61.1)	.18	54 (50.9)	55 (61.1)	.18
No. of tumors: Median [IQR]	1 [1-3]	1 [1-2]		1 [1-2]	1 [1-1]	<.01	1 [1-3]	1 [1-2]	.09	1 [1-1]	1 [1-2]	.01
Gross vascular invasion	195 (19.5)	36 (18.4)	.75	126 (18.0)	23 (21.7)	.32	69 (23.0)	13 (14.4)	.09	23 (21.7)	13 (14.4)	.194
Metastasis	82 (8.2)	10 (5.1)	.124	48 (6.9)	4 (3.8)	.22	34 (11.9)	6 (6.7)	.16	4 (3.8)	6 (6.7)	.393
Patient and laboratory variables												
Age: Median [IQR], y	60 [55-66]	60 [55-64]	.25	59 [54-66]	60 [54-64]	.55	62 [56-66]	60 [55-65]	.07	60 [54-64]	60 [55-65]	.29
Commercial insurance	366 (36.6)	61 (31)	.14	286 (40)	40 (37.7)	.53	87 (29.0)	21 (23.0)	.29	40 (37.7)	21 (23.0)	.04
INR: Median [IQR]	1.2 [1.1-1.4]	1.1 [1.0-1.3]	<.01	1.2 [1.1-1.4]	1.1 [1.1-1.3]	.02	1.1 [1.0-1.3]	1.0 [1.0-1.2]	.34	1.1 [1.1-1.3]	1.1 [1.0-1.2]	.09
Platelets: Median [IQR], $10^3/mm^3$	113 [74-168]	136 [90-185]	<.01	101 [68-154]	123 [80-170]	<.01	136 [96-198]	149 [106-203]	.31	123 [80-170]	149 [106-203]	<.01
Bilirubin: Median [IQR], mg/dL	1.1 [0.7-2.1]	0.8 [0.6-1.4]	<.01	1.2 [0.8-2.2]	0.9 [0.6-1.6]	<.01	0.9 [0.6-1.6]	0.8 [0.5-1.3]	.02	0.9 [0.6-1.6]	0.8 [0.5-1.3]	.15
Albumin: Median [IQR], g/dL	3.4 [2.9-3.8]	3.5 [3.0-4.0]	.02	3.3 [2.9-3.8]	3.6 [2.9-4.1]	.01	3.4 [2.9-3.9]	3.4 [3.0-3.9]	.64	3.6 [2.9-4.1]	3.4 [3.0-3.9]	.10
FIB-4 score: Median [IQR]	6.2 [3.7-10.0]	4.7 [3.1-7.4]	<.01	6.7 [4.1-10.6]	5.5 [3.4-8.9]	.02	4.9 [3.0-8.2]	3.6 [2.6-6.7]	.01	5.5 [3.4-8.9]	3.6 [2.6-6.7]	<.01
MELD score: Median [IQR]	10 [7-16]	8 [7-14]	<.01	10 [7-16]	9 [7-14]	<.01	9 [7-14]	8 [7-14]	.08	9 [7-14]	8 [7-14]	.90
Child-Pugh score												
A	599 (59.9)	141 (71.9)	<.01	401 (57.3)	71 (67.0)	.04	198 (66.7)	70 (77.8)	.04	71 (67.0)	70 (77.8)	.09
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)	

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; FIB-4 score, Fibrosis-4 Index for Liver Fibrosis score; HIV, human immunodeficiency virus; INR, international normalized ratio; IQR, interquartile range; MELD, Model End-Stage Liver Disease.

[a]Categorical variables are reported as total numbers (%), and continuous variables are reported as medians (IQRs).

TABLE 9. Hepatitis C Virus Monoinfection: Liver Function on Diagnosis and Tumor Radiologic and Pathologic Characteristics[a]

Characteristic	No. of Patients (%)		
	Non-Black, n = 314	Black, n = 117	*P*
Age: Median [IQR], y	59 [54-66]	53 [57-68]	<.01
Insurance	137 (43.6)	32 (27.3)	<.01
Liver function on diagnosis			
INR: Median [IQR]	1.2 [1.1-1.4]	1.1 [1-1.3]	.02
Platelets: Median [IQR], 10^3/mm^3	99 [67-144]	135 [100-196]	<.01
Total bilirubin: Median [IQR], mg/dL	1.2 [0.7-2.3]	1.1 [0.6-1.7]	.03
Albumin: Median [IQR], g/dL	3.3 [2.9-3.8]	3.4 [2.8-3.8]	.93
MELD score: Median [IQR]	6.6 [4.1-10.6]	5.6 [3.2-8.1]	.01
Child-Pugh score			.56
A	182 (58.0)	73 (62.4)	
B	89 (28.3)	32 (27.4)	
C	43 (13.7)	12 (10.2)	
FIB-4 score: Median [IQR]	6.6 [4.1-10.6]	5.6 [3.2-8.1]	.01
FIB-4 score <3.25	57 (18.2)	31 (26.5)	.05
Tumor imaging characteristic			
Within Milan criteria	195 (62.3)	61 (52.1)	.05
BCLC staging			.06
A	178 (57.1)	58 (50.4)	
B	43 (13.8)	16 (13.9)	
C	48 (15.4)	30 (26.1)	
D	43 (13.8)	11 (9.6)	
Tumor size: Median [IQR], cm	2.9 [2.1-4.8]	3.5 [2.1-5.8]	.19
Tumor size >2.5 cm	180 (59.8)	69 (63.9)	.46
No. of tumors: Median [IQR]	1 [1-2]	1 [1-2]	.56
Gross vascular invasion	51 (16.3)	28 (23.9)	.07
Metastasis	20 (6.6)	14 (12.2)	.05
	Resected/Transplanted Patients, No. (%)		
Pathologic Report	Non-Black, n = 129	Black, n = 33	*P*
Microvascular invasion	68 (52.7)	26 (78.8)	<.01
Nodules/satellite lesions	53 (41.7)	18 (58.1)	.10
Poor differentiation	25 (19.3)	8 (24.2)	.62
Pathologic AJCC TNM stage I	27 (16.7)	1 (3.0)	.01

Abbreviations: AJCC TNM, American Joint Committee on Cancer tumor, lymph node, metastasis classification; BCLC, Barcelona Clinic Liver Cancer; FIB-4 score, Fibrosis-4 Index for Liver Fibrosis score; INR, international normalized ratio; MELD, Model End-Stage Liver Disease.
[a]The analysis excluded patients who had hepatitis B virus exposure, HIV-positive status, and no information about hepatitis B viral status.

and 5-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; and 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 had vascular invasion, Black patients were less likely to be within Milan criteria, limiting treatment options.[38]

It is unclear the extent to which these characteristics reflect a distinctive molecular profile that confers an inherently more aggressive phenotype and diagnosis at a more advanced stage of disease because of delayed diagnosis. Black patients were less likely to have commercial insurance, as observed in previous studies,[21] raising the possibility that barriers to accessing health care services may have contributed to delays in HCC diagnosis. However, they were also likely to meet screening criteria; therefore, Black patients 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 American Association for the Study of Liver

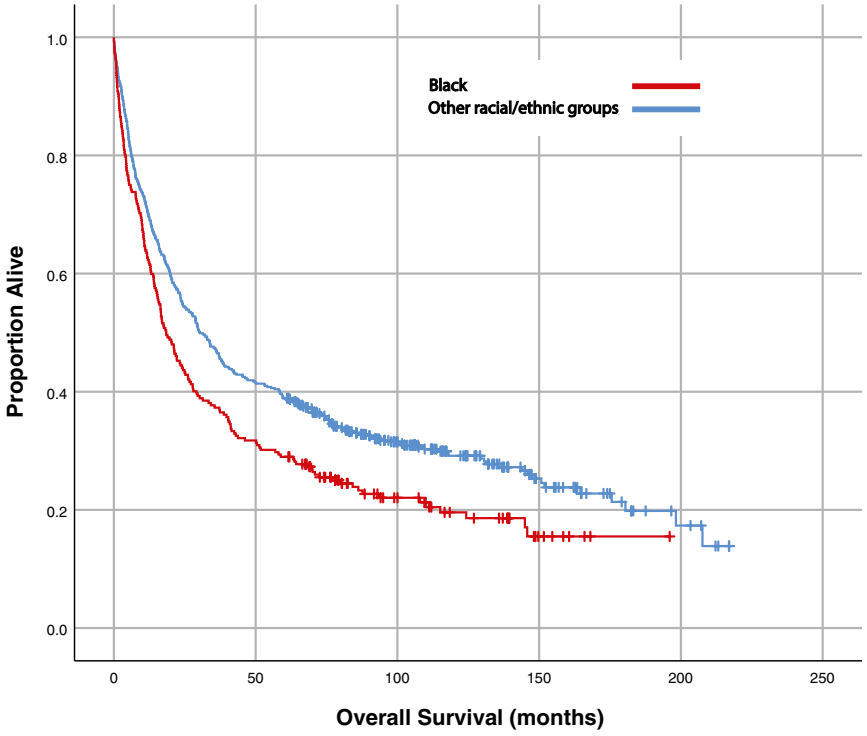

Figure 3. Kaplan-Meier curves illustrate the overall survival of patients with hepatocellular carcinoma according to racial/ethnic group ($P < .01$).

Disease guidelines, patients with cirrhosis should have life-long, twice-annual HCC surveillance.[20,21] As previously described, an FIB-4 score >3.25 correlates with advanced fibrosis and cirrhosis.[26,27] Nearly one-third of the Black patients in our cohort had an FIB-4 score <3.25. Because of this, their need for HCC surveillance may have been underestimated by the patients and their health care providers. Moreover, one-half of the Black patients did not have any features of cirrhosis on imaging that could have been another trigger for HCC screening by the health care provider. Practice guidelines recommending HCC surveillance for cirrhotic patients with HCV 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 demonstrated that a surveillance program using AFP and liver ultrasound performed every 6 months resulted in a 37% reduction in HCC mortality. As noted previously, Black patients with HCC have lower levels of AFP.[39] Our current results corroborate this finding; one-third of our Black patients had AFP values <10 ng/mL. Therefore, 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 coinfection 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.[40-43] Kubo et al[44] reported that HCC was more likely to develop in noncirrhotic livers among patients with HCV RNA and anti-HBcAb than in patients with HCV RNA and no evidence of HBV exposure. Matsuoka et al[41] 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.[45] In our study, patients with HBV exposure had higher scores for fibrosis stage. Kubo et al[44] reported that patients with HCV and anti-HBc antibodies had less well differentiated tumors, but the tumors were similar in size. In our study, patients with prior HBV infection had larger tumors, and lower percentages 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 from

studies performed during the early years of antiretroviral therapy.[46] 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 health care; 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 their HCCs had worse prognostic features, indicating that the HCC profile identified in this study (ie, relatively well preserved liver function and more aggressive tumors) is characteristic of HCC in HCV-infected Black patients and is not because of 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 noncirrhotic livers, specifically exploring germline and somatic mutations,[45-49] toxic exposures (air pollution, alcohol,[50] and cigarette smoke[51]), and comorbidities, such as type II diabetes.[52,53]

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.[30] 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. In addition, 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 in which 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 or subtype that may guide targeted treatment. Our results also reveal the need to revise current HCC surveillance criteria to include noncirrhotic 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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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Tali Shaltiel: Conceptualization, data curation, formal analysis, writing–original draft, and reviewed and approved the final version. **Serena Zheng:** Data curation and reviewed and approved the final version. **Cleo Siderides:** Data curation and reviewed and approved the final version. **Elizabeth M. Gleeson:** Formal analysis and reviewed and approved the final version. **Jacquelyn Carr:** Writing–review and editing and reviewed and approved the final version. **Eric R. Pletcher:** Data curation and reviewed and approved the final version. **Noah A. Cohen:** Writing–review and editing and reviewed and approved the final version. **Benjamin J. Golas:** Reviewed and approved the final version. **Deepa R. Magge:** Reviewed and approved the final version. **Daniel M. Labow:** Reviewed and approved the final version. **Andrea D. Branch:** Conceptualization and reviewed and approved the final version. **Umut Sarpel:** Conceptualization, writing–original draft, and reviewed and approved the final version.

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