Liver Cancer Has a Distinctive Profile in Black Patients: Current Screening Guidelines May Be Inadequate

Liver cancer is often deadly, but the chances of survival can be improved by early detection, which opens the door for curative treatments, such as resection and liver transplantation. Mortality varies across sociodemographic groups for reasons that are complex and multifactorial. In the United States, Black patients are both more likely to develop hepatocellular carcinoma (HCC) and more likely to die because of it. A recent publication in the March 2021 issue of *Cancer*[1] by our group at the Icahn School of Medicine at Mount Sinai adds important new evidence that HCC has a distinctive profile in Black individuals.[2-9]

Abbreviations: FIB-4, fibrosis-4; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

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The risk of developing HCC is much higher in patients who have an underlying liver disease, such as viral hepatitis or alcohol-associated liver disease. Chronic liver disease causes inflammation, genetic damage to liver cells, and fibrosis, which can progress to cirrhosis. In most Western populations, the great majority of HCC (~90%) arises in patients with established cirrhosis. Importantly, cirrhosis is not a homogeneous or stable disease state but rather one that spans a wide range of severity and may progress over time. Patients with early cirrhosis are largely asymptomatic, while patients with decompensated cirrhosis are subject to variceal bleeding, ascites, and encephalopathy. Surveillance guidelines of the American Association for the Study of Liver Diseases recommend life-long, twice-annual, abdominal imaging for patients with cirrhosis but recommend against screening for most patients without cirrhosis.[10] However, it is becoming increasingly clear that current surveillance recommendations may need to be extended to include Black patients who have not developed cirrhosis.

Our latest study builds on our previous investigations of patients with hepatitis C virus (HCV) infection, the most common chronic liver disease in people who die from liver cancer in the United States. It was carried out on 1,195 patients with HCC, 390 of whom self-identified as Black. This study reported that HCC in Black individuals had a distinctive profile compared to HCC in other patients (Table 1). At the time of HCC diagnosis, Black patients had greater liver function, as indicated by lower serum total bilirubin and international normalized ratio. Further, they had fewer abnormalities that result from cirrhosis, such as architectural changes in the liver, ascites, splenomegaly, low platelet counts, and other radiologic features of portal hypertension. Thirty-one percent of Black patients had a fibrosis-4 (FIB-4) score below 3.25 (a threshold indicating advanced fibrosis/cirrhosis) compared to 18% of patients who were not Black. This

TABLE 1. DIFFERENCES IN CLINICOPATHOLOGIC PROFILES BETWEEN BLACK AND NON-BLACK PATIENTS AT THE TIME OF HCC DIAGNOSIS

	Estevez et al.[4]		Jones et al.[3]		Rich et al.[5]		Shaltiel et al.[1]		Winters et al.[2]	
	White	Black	White	Black	White	Black	Non-Black	Black	Non-Black	Black
Total bilirubin, median [IQR or SD], mg/dL	1.73 [0.7-1.9]	1.63 [0.6-1.7]	1.4 [0.8-2.6]	0.9 [0.6-2]	2.1 [3.7]*	1.7 [2.5]*	1.20 [0.7-2.2]*	0.90 [0.6-1.5]*	1.9 [2.47]†	1.02 [0.86]†
Platelet [IQR or SD], $\times 10^3$	138 [76-174]†	155 [89-193]†	104 [70-168]	166 [116-264]	135 [88]†	175 [102]†	105 [69-155]*	144 [100-202]*	99.4 [61.7]*	128.6 [64.7]*
Albumin, median [IQR or SD] g/dL	3.58 [0.64]†	3.4 [0.72]†	3.2 [2.8-3.9]	3.6 [3.1-4]	—	—	3.4 [2.9-3.8]	3.4 [2.95-3.8]	3.3 [0.65]*	3.6 [0.59]*
INR, median [IQR or SD]	1.22 [0.3]	1.23 [0.32]	1.2[1.1-1.4]	1.2 [1.1-1.4]	—	—	1.2 [1.1-1.4]*	1.1 [1-1.3]*	1.26 [0.35]*	1.12 [0.19]*
FIB-4 [IQR or SD]	—	—	—	—	—	—	6.54 [3.99-10.53]*	4.66 [2.94-7.52]*	9.2 [7.6]*	6.5 [5.1]*
Pathologic liver fibrosis stage 4, n (%)	—	—	364 (87.9%)	104 (77%)	—	—	187 (80.3)*	68 (63.6)*	—	—

*Statistical significance at $P < 0.05$.
†Statistical significance at $P < 0.001$.
Abbreviations: INR, international normalized ratio; IQR, interquartile range.

study was the second from our group to demonstrate a significantly lower FIB-4 in Black individuals; this novel finding has not been reported by other groups. Because they lacked many of the characteristic indicators of more advanced liver disease, Black patients and their health care providers may have underestimated their HCC risk.

In contrast to the more favorable liver characteristics at the time of HCC diagnosis, tumors in Black patients were more aggressive and the cancers were more advanced. Tumors were larger and more likely to be multifocal, poorly differentiated, and to have metastasized. Black patients were more likely to be outside Milan criteria and to have disease that was too advanced for them to be considered for resection or liver transplantation, the only potentially curative therapies. Black patients had shorter median survival (18 months versus 30 months) and were less likely to survive 5 years. Many factors may have contributed to the worse outcomes. Black patients were less likely to have commercial insurance, which may be a barrier to health care. They also had lower levels of serum alpha fetoprotein; an important biomarker used by many in conjunction with imaging for HCC screening, which may have led to a delay in diagnosis.

The distinctive profile of HCC in Black patients (less advanced liver disease more advanced tumors) was investigated in the following three subgroups of patients exposed to HCV: (1) those with HCV and human immunodeficiency virus (HIV), (2) those with HCV and hepatitis B virus (HBV), and (3) those with HCV in the absence of HIV or HBV. The overall profile was the same in all three groups. This distinctive profile of HCC in Black patients has two important take away messages, one in the domain of clinical management and the other in the domain of basic and translational research. Regarding clinical management, the findings indicate that Black individuals exposed to HCV may benefit from initiating liver cancer surveillance before they develop cirrhosis. This could increase the likelihood that liver cancer would be diagnosed at an early and curable stage. The findings also suggest that the environmental, cellular, genetic, and immunologic factors leading to HCC in Black patients may be somewhat different from the risk factors in other patients.

The latest research adds to what is known from other studies at Mount Sinai[2] and elsewhere

(Table 1).[3-5] An investigation of HCC in patients infected with HBV receiving care in the Veterans Administration showed that most of the patients who lacked cirrhosis (16 of 30) were Black.[6] Jones et al.[3] performed a tri-institutional study of a diverse population of patients with HCC with a variety of liver diseases who were receiving care in the greater Miami metropolitan area. They observed that Black patients with HCC had less advanced liver disease (as evidenced by higher platelet count, lower total bilirubin, and higher serum albumin) but worse tumor characteristics and found that Black patients had the shortest survival of any group examined. Researchers conducting a second large multicenter study had similar findings. At the time of HCC diagnosis, Black patients had significantly lower rates of liver cirrhosis and decompensated disease yet more advanced liver cancer.[4] These investigators found that Black patients had poorer survival than other racial/ethnic groups after 2010.

In another study of patients with HCC receiving care at two large health systems in Texas, Rich et al.[5] found that Black patients had less ascites, less hepatic encephalopathy, a lower total bilirubin, and a higher platelet count at the time of diagnosis. In a comparison of White, Hispanic, and Black patients treated at a single center in Chicago, Black patients were least likely to have HCC within Milan criteria and had the highest rate of portal vein invasion.[7] The authors found that Black patients, when compared to White and Hispanic individuals, had significantly lower Model for End-Stage Liver Disease (MELD) scores at the time of diagnosis as well as the lowest rates of encephalopathy and ascites. In another single-center study comparing 164 Black and 1,032 White patients with HCC, Dakhoul et al.[8] found that Black patients had a significantly higher mean platelet count and trended toward larger tumors, but they found no difference in MELD score or in the proportion of patients within Milan criteria. Finally, a small study of patients with various liver diseases (but not with HCV infection) conducted at Mount Sinai also suggested that HCC in Black patients has a distinctive profile of better compensated liver disease yet more aggressive liver cancer, with significantly larger median tumor size, higher rates of vascular invasion, and a lower proportion presenting within Milan criteria.[9]

The findings from multiple studies from across the United States are strikingly consistent. They make a compelling case that current surveillance guidelines may not be ideal for Black individuals and indicate the need for future research to define HCC risk in Black patients. Underlying these findings is the inextricable presence of racial disparities across the spectrum of care for liver cancer. For example, other studies have found Black patients with HCC are less likely to receive surgery[11] or undergo liver transplantation.[12]

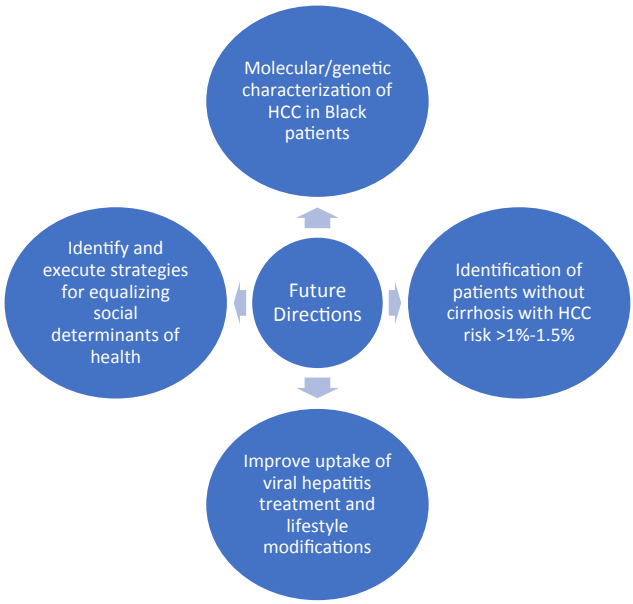

FIG. 1. Future directions.

Future Direction

Further research is needed in four areas (Fig. 1). First, detailed cell and molecular studies are needed to characterize HCCs in Black patients and to determine whether their tumors have distinctive mutations and/or immunologic features that could be targeted with precision interventions. Second, outcomes research is needed to define the group of patients without cirrhosis whose HCC risk is above 1.0%-1.5% (the threshold for cost-effective HCC surveillance). Such research must identify the specific exposures that elevate HCC risk in Black individuals, recognizing that genetic, environmental, sociodemographic, and lifestyle differences may all be important. Third, implementation and basic research are needed to improve strategies for preventing liver cancer, which is a largely preventable

cause of death. Specifically, implementation research is needed to improve uptake of treatments for viral hepatitis and for lifestyle modifications, including smoking cession and moderation of alcohol consumption. Basic research is needed to delineate and harness liver repair pathways, allowing the safe reversal of liver damage. Overall, we must strive to understand and correct the social and economic inequities that contribute to poor health and create durable and impactful solutions.

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