

The Effect of Race on Outcomes in Veterans With Hepatocellular Carcinoma at a Single Center

Jackson Reynolds, MD^a; Sarah Hashimi, MD^a; Ngan Nguyen, DO^a; Jordan Infield MD^{a,b}; Alva Weir, MD^{a,c}; and Amna Khattak, MD^{a,c}

Background: Black patients have a higher incidence and mortality associated with hepatocellular carcinoma (HCC) compared with that of White patients in many retrospective analyses. This study sought to determine whether veterans treated for HCC at the Memphis Veterans Affairs Medical Center (VAMC) in Tennessee showed similar disparities in terms of stage at diagnosis, type of therapy received, and overall survival (OS).

Methods: A retrospective review evaluated 132 White and 95 Black patients treated for HCC between 2009 and 2021. We evaluated the impact on OS of age, sex, comorbidities, tumor stage, α -fetoprotein level, method of diagnosis, first-line treatment, systemic treatment, and surgical options offered. Kaplan-Meier analysis was used to investigate differences in OS and cumulative hazard ratio for death. Cox regression multivariate analysis evalu-

ated discrepancies among investigated variables.

Results: The study found no significant difference in OS between Black and White veterans with HCC. Significant differences were found in who received surgical treatment and systemic therapy. More White veterans received any form of treatment compared with Black veterans ($P < .001$), and White veterans were more likely to undergo surgical resection and transplant ($P = .052$). There was no significant difference between age or stage at diagnosis, receipt of systemic therapy, alcohol, tobacco or drug use, HIV coinfection, or cirrhosis.

Conclusions: Black veterans with HCC at the Memphis VAMC were less likely to receive any form of treatment, surgical resection, or transplant compared with White veterans, but this did not have a statistically significant effect on OS.

Author affiliations can be found at the end of this article.

Correspondence:

Jackson Reynolds
(jreyno54@uthsc.edu)

Fed Pract. 2022;39(suppl 3).
Published online August 13.
doi:10.12788/tp.0304

Hepatocellular carcinoma (HCC) is the sixth most common and third most deadly malignancy worldwide, carrying a mean survival rate without treatment of 6 to 20 months depending on stage.¹ Fifty-seven percent of patients with liver cancer are diagnosed with regional or distant metastatic disease that carries 5-year relative survival rates of 10.7% and 3.1%, respectively.² HCC arises most commonly from liver cirrhosis due to chronic hepatocyte injury, which may be mediated by viral hepatitis, alcoholism, and metabolic disease. Other less common causes include autoimmune disease, exposure to environmental hazards, and certain genetic diseases, such as α -1 antitrypsin deficiency and Wilson disease.

Multiple staging systems for HCC exist that incorporate some variation of the following features: size and invasion of the tumor, distant metastases, and liver function. Stage-directed treatments for HCC include ablation, embolization, resection, transplant, and systemic therapy, such as tyrosine kinase inhibitors, immunotherapies, and monoclonal antibodies. In addition to tumor/node/metastasis (TNM) staging, α -fetoprotein (AFP) is a diagnostic marker with prognostic value in HCC with higher levels correlating to higher tumor burden and a worse prognosis. With treatment, the 5-year survival rate for early stage HCC ranges from 60% to 80% but decreases significantly with higher stages.¹ HCC

screening in at-risk populations has accounted for > 40% of diagnoses since the practice became widely adopted, and earlier recognition has led to an improvement in survival even when adjusting for lead time bias.³

Systemic therapy for advanced disease continues to improve. Sorafenib remained the standard first-line systemic therapy since it was introduced in 2008.⁴ First-line therapy improved with immunotherapies. The phase 3 IMBrave150 trial comparing atezolizumab plus bevacizumab to sorafenib showed a median overall survival (OS) > 19 months with 7.7% of patients achieving a complete response.⁵ HIMALAYA, another phase 3 trial set for publication later this year, also reported promising results when a priming dose of the CTLA-4 inhibitor tremelimumab followed by durvalumab was compared with sorafenib.⁶

There has been a rise in incidence of HCC in the United States across all races and ethnicities, though Black, Hispanic, and Asian patients remain disproportionately affected. Subsequently, identifying causative biologic, socioeconomic, and cultural factors, as well as implicit bias in health care continues to be a topic of great interest.⁷⁻⁹ Using Surveillance, Epidemiology, and End Results (SEER) data, a number of large studies have found that Black patients with HCC were more likely to present with an advanced stage, less likely to receive

curative intent treatment, and had significantly reduced survival compared with that of White patients.^{1,7-9} An analysis of 1117 patients by Rich and colleagues noted a 34% increased risk of death for Black patients with HCC compared with that of White patients, and other studies have shown about a 50% reduction in rate of liver transplantation for Black patients.¹⁰⁻¹² Our study aimed to investigate potential disparities in incidence, etiology, AFP level at diagnosis, and outcomes of HCC in Black and White veterans managed at the Memphis Veterans Affairs Medical Center (VAMC) in Tennessee.

METHODS

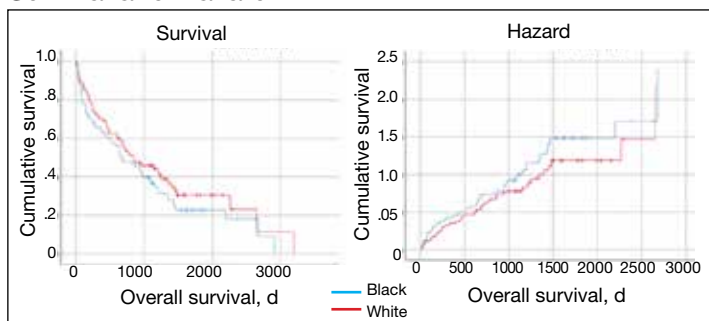
A single center retrospective chart review was conducted at the Memphis VAMC using the Computerized Patient Record System (CPRS) and the *International Statistical Classification of Diseases, Tenth Revision (ICD-10)* code C22.0 for HCC. Initial results were manually refined by pre-specified criteria. Patients were included if they were diagnosed with HCC and received HCC treatment at the Memphis VAMC. Patients were excluded if HCC was not diagnosed histologically or clinically by imaging characteristics and AFP level, if the patient's primary treatment was not provided at the Memphis VAMC, if they were lost to follow-up, or if race was not specified as either Black or White.

The following patient variables were examined: age, sex, comorbidities (alcohol or substance use disorder, cirrhosis, HIV), tumor stage, AFP, method of diagnosis, first-line treatments, systemic treatment, surgical options offered, and mortality. Staging was based on the American Joint Committee on Cancer TNM staging for HCC.¹³ Surgical options were recorded as resection or transplant. Patients who were offered treatment but lost to follow-up were excluded from the analysis.

Data Analysis

Our primary endpoint was identifying differences in OS among Memphis VAMC patients with HCC related to race. Kaplan-Meier analysis was used to investigate differences in OS and cumulative hazard ratio (HR) for death. Cox regression multivariate analysis further evaluated discrepancies among investigated patient variables, including age, race, alcohol, tobacco, or illicit drug use, HIV coinfection, and cirrhosis. Treatment factors were further defined by first-line treatment, systemic therapy, surgical re-

FIGURE Kaplan-Meier Estimates for Overall Cumulative Survival and Hazard



Overall survival was 41.0 mo (1247 d) for Black veterans compared with 33.9 mo (1032 d) for White veterans ($P = .24$).

TABLE 1 Overall Survival for Hepatocellular Carcinoma

Group	Overall survival (95% CI), d
Black	1032 (792-1273)
White	1247 (967-1526)

section, and transplant. χ^2 analysis was used to investigate differences in treatment modalities.

RESULTS

We identified 227 veterans, 95 Black and 132 White, between 2009 and 2021 meeting criteria for primary HCC treated at the Memphis VAMC. This study did not show a significant difference in OS between White and Black veterans ($P = .24$). Kaplan-Meier assessment showed OS was 1247 days (41 months) for Black veterans compared with 1032 days (34 months) for White veterans (Figure; Table 1).

Additionally, no significant difference was found between veterans for age or stage at diagnosis when stratified by race. The mean age of diagnosis for both groups was 65 years ($P = .09$). The mean TNM staging was 1.7 for White veterans vs 1.8 for Black veterans ($P = .57$). There was a significant increase in the AFP level at diagnosis for Black veterans ($P = .001$) (Table 2).

The most common initial treatment for both groups was transarterial chemoembolization and radiofrequency ablation with 68% of White and 64% of Black veterans receiving this therapy. There was no significant difference between who received systemic therapy.

However, we found significant differences by race for some forms of treatment. In our analysis, significant differences existed between those who did not receive any form of treatment as well

TABLE 2 Baselines Demographics

Variables	White race	Black race	P value
Age, mean (95% CI), y	65 (63.6-66.6)	65 (63.7-65.8)	.09
Stage, mean (95% CI) ^a	1.7 (1.4-1.8)	1.8 (1.5-2.1)	.57
α-fetoprotein level, mean (95% CI), ng/mL	234 (83.6-469.5)	1810 (378.7-3739.9)	.001

^aAmerican Joint Committee on Cancer tumor/node/metastasis staging for hepatocellular cancer.

TABLE 3 Multivariate Analysis for Factors Affecting Survival

Variable	Hazard ratio (95% CI)	P value
Age		
≥ 65 y	0.95 (0.64-1.41)	.80
< 65 y	1.05 (0.7162-1.54)	.80
Race		
Black	1.30 (0.87-1.94)	.20
White	0.77 (0.51-1.15)	.20
Comorbidities		
Alcohol use	0.98 (0.60-1.65)	.98
Tobacco use	1.37 (0.78-2.41)	.27
Illicit drug use	0.86 (0.55-1.37)	.53
HIV coinfection	1.55 (0.36-6.62)	.56
Liver cirrhosis	1.25 (0.68-2.30)	.47
α-fetoprotein level > 400 ^a	1.36 (0.65-1.46)	.01

^aAssociated with significant negative survival outcome.

as who received surgical resection and transplant. Among Black veterans, 11.6% received no treatment vs 6.1% for White veterans ($P = .001$). Only 2.1% of Black veterans underwent surgical resection vs 8.3% of White veterans ($P = .046$). Similarly, 13 (9.8%) White veterans vs 3 (3.2%) Black veterans received orthotopic liver transplantation ($P = .052$) in our cohort (eAppendix available at doi:10.12788/fp.0304). We found no differences in patient characteristics affecting OS, including alcohol use, tobacco use, illicit drug use, HIV coinfection, or liver cirrhosis (Table 3).

DISCUSSION

In this retrospective analysis, Black veterans with HCC did not experience a statistically significant decrease in OS compared with that of White veterans despite some differences in therapy offered. Other studies have found that surgery was less frequently recommended to Black patients across multiple cancer types, and in most cases this carried a negative impact on OS.^{8,10,11,14,15} A number of other studies have demonstrated a greater percentage of Black patients receiving no treatment, although these studies are often based on SEER data, which captures only cancer-directed surgery and no other methods of treat-

ment. Inequities in patient factors like insurance and socioeconomic status as well as willingness to receive certain treatments are often cited as major influences in health care disparities, but systemic and clinician factors like hospital volume, clinician expertise, specialist availability, and implicit racial bias all affect outcomes.¹⁶ One benefit of our study was that CPRS provided a centralized recording of all treatments received. Interestingly, the treatment discrepancy in our study was not attributable to a statistically significant difference in tumor stage at presentation. There should be no misconception that US Department of Veterans Affairs patients are less affected by socioeconomic inequities, though still this suggests clinician and systemic factors were significant drivers behind our findings.

This study did not intend to determine differences in incidence of HCC by race, although many studies have shown an age-adjusted incidence of HCC among Black and Hispanic patients up to twice that of White patients.^{1,8-10} Notably, the rate of orthotopic liver transplantation in this study was low regardless of race compared with that of other larger studies of patients with HCC.^{12,15} Discrepancies in HCC care among White and Black patients have been suggested to stem from a variety of influences, including access to early diagnosis and treatment of hepatitis C virus, comorbid conditions, as well as complex socioeconomic factors. It also has been shown that oncologists' implicit racial bias has a negative impact on patients' perceived quality of communication, their confidence in the recommended treatment, and the understood difficulty of the treatment by the patient and should be considered as a contributor to health disparities.^{17,18}

Studies evaluating survival in HCC using SEER data generally stratify disease by localized, regional, or distant metastasis. For our study, TNM staging provided a more accurate assessment of the disease and reduced the chances that broader staging definitions could obscure differences in treatment choices. Future studies could be improved by stratifying patients by variables impacting treatment choice, such as Child-Pugh score or Barcelona Clinic Liver Cancer staging. Our study demonstrated a statistically significant difference in AFP level between White and Black veterans. This has been observed in prior studies as well, and while no specific cause has been identified, it suggests differences in tumor biologic features across different races. In addition, we found that an elevated AFP level

at the time of diagnosis (defined as > 400) correlates with a worsened OS (HR, 1.36; $P = .01$).

Limitations

This study has several limitations, notably the number of veterans eligible for analysis at a single institution. A larger cohort would be needed to evaluate for statistically significant differences in outcomes by race. Additionally, our study did not account for therapy that was offered to but not pursued by the patient, and this would be useful to determine whether patient or practitioner factors were the more significant influence on the type of therapy received.

CONCLUSIONS

This study demonstrated a statistically significant difference in the rate of resection and liver transplantation between White and Black veterans at a single institution, although no difference in OS was observed. This discrepancy was not explained by differences in tumor staging. Additional, larger studies will be useful in clarifying the biologic, cultural, and socioeconomic drivers in HCC treatment and mortality.

Acknowledgments

The authors thank Lorri Reaves, Memphis Veterans Affairs Medical Center, Department of Hepatology.

Author affiliations

^aThe University of Tennessee Health Science Center, Memphis

^bDuke University Health System, Durham, North Carolina

^cMemphis Veterans Affairs Medical Center, Tennessee

Author disclosures

The authors report no actual or potential conflicts of interest or outside sources of funding with regard to this article.

Disclaimer

The opinions expressed herein are those of the authors and do not necessarily reflect those of *Federal Practitioner*, Frontline Medical Communications Inc., the US Government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review the complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.

Ethics and consent

This study was approved by the Memphis Veterans Affairs Institutional Review Board.

References

- Altekruze SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol*. 2009;27(9):1485-1491. doi:10.1200/JCO.2008.20.7753
- Howlader N, Noone AM, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Accessed July 8, 2022. https://seer.cancer.gov/archive/csr/1975_2012/results_merged/sect_14_liver_bile.pdf#page=8
- Singal AG, Mittal S, Yerokun OA, et al. Hepatocellular carcinoma screening associated with early tumor detection and improved survival among patients with cirrhosis in the US. *Am J Med*. 2017;130(9):1099-1106.e1. doi:10.1016/j.amjmed.2017.01.021
- Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359(4):378-390. doi:10.1056/NEJMoa0708857
- Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894-1905. doi:10.1056/NEJMoa1915745
- Abou-Alfa GK, Chan SL, Kudo M, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA. *J Clin Oncol*. 2022;40(suppl 4):379. doi:10.1200/JCO.2022.40.4_suppl.379
- Franco RA, Fan Y, Jarosek S, Bae S, Galbraith J. Racial and geographic disparities in hepatocellular carcinoma outcomes. *Am J Prev Med*. 2018;55(5)(suppl 1):S40-S48. doi:10.1016/j.amepre.2018.05.030
- Ha J, Yan M, Aguilar M, et al. Race/ethnicity-specific disparities in hepatocellular carcinoma stage at diagnosis and its impact on receipt of curative therapies. *J Clin Gastroenterol*. 2016;50(5):423-430. doi:10.1097/MCG.0000000000000448
- Wong R, Corley DA. Racial and ethnic variations in hepatocellular carcinoma incidence within the United States. *Am J Med*. 2008;121(6):525-531. doi:10.1016/j.amjmed.2008.03.005
- Rich NE, Hester C, Odewole M, et al. Racial and ethnic differences in presentation and outcomes of hepatocellular carcinoma. *Clin Gastroenterol Hepatol*. 2019;17(3):551-559.e1. doi:10.1016/j.cgh.2018.05.039
- Peters NA, Javed AA, He J, Wolfgang CL, Weiss MJ. Association of socioeconomic, surgical therapy, and survival of early stage hepatocellular carcinoma. *J Surg Res*. 2017;210:253-260. doi:10.1016/j.jss.2016.11.042
- Wong RJ, Devaki P, Nguyen L, Cheung R, Nguyen MH. Ethnic disparities and liver transplantation rates in hepatocellular carcinoma patients in the recent era: results from the Surveillance, Epidemiology, and End Results registry. *Liver Transpl*. 2014;20(5):528-535. doi:10.1002/lt.23820
- Minagawa M, Ikai I, Matsuyama Y, Yamaoka Y, Makuuchi M. Staging of hepatocellular carcinoma: assessment of the Japanese TNM and AJCC/UICC TNM systems in a cohort of 13,772 patients in Japan. *Ann Surg*. 2007;245(6):909-922. doi:10.1097/01.sla.0000254368.65878.da
- Harrison LE, Reichman T, Koneru B, et al. Racial discrepancies in the outcome of patients with hepatocellular carcinoma. *Arch Surg*. 2004;139(9):992-996. doi:10.1001/archsurg.139.9.992
- Sloane D, Chen H, Howell C. Racial disparity in primary hepatocellular carcinoma: tumor stage at presentation, surgical treatment and survival. *J Natl Med Assoc*. 2006;98(12):1934-1939.
- Haider AH, Scott VK, Rehman KA, et al. Racial disparities in surgical care and outcomes in the United States: a comprehensive review of patient, provider, and systemic factors. *J Am Coll Surg*. 2013;216(3):482-92.e12. doi:10.1016/j.jamcollsurg.2012.11.014
- Cooper LA, Roter DL, Carson KA, et al. The associations of clinicians' implicit attitudes about race with medical visit communication and patient ratings of interpersonal care. *Am J Public Health*. 2012;102(5):979-987. doi:10.2105/AJPH.2011.300558
- Penner LA, Dovidio JF, Gonzalez R, et al. The effects of oncologist implicit racial bias in racially discordant oncology interactions. *J Clin Oncol*. 2016;34(24):2874-2880. doi:10.1200/JCO.2015.66.3658

eAPPENDIX Hepatocellular Carcinoma Therapies^a

Therapies	Black race, No. (%) (n = 95)	White race, No. (%) (n = 132)	P value
No treatment	11 (11.6)	8 (6.1)	.001
Transarterial chemoembolization	59 (62.1)	77 (58.3)	
Systemic therapy (sorafenib)	12 (12.6)	16 (12.1)	.73
Surgical resection	2 (2.1)	11 (8.3)	.046
Transplant	3 (3.2)	13 (9.8)	.052
Yttrium-90	4 (4.2)	2 (1.5)	--
Radiofrequency ablation	2 (2.1)	5 (3.8)	--
Stereotactic body radiotherapy	2 (2.1)	0 (0)	--

^aPatients lost to follow-up were excluded from the study.