**Name of Journal:** *World Journal of Hepatology*

**Manuscript NO:** 40116

**Manuscript Type:** ORIGINAL ARTICLE

***Retrospective Study***

**African Americans are less likely to receive curative treatment for hepatocellular carcinoma**

Sobotka LA *et al.* African Americans are less likely to receive curative treatment for HCC

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**Author contributions:** All authors helped to perform the research; Sobotka LA performed conception and design of the study, interpretation of data, drafting the article and final approval of the version of the article to be published; Hinton A performed acquisition of data, analysis of data, critical revisions related to important intellectual content of the manuscript and final approval of the article to be published; Conteh LF performed conception and design of the study, interpretation of data, drafting the article, critical revisions related to important intellectual content of the manuscript, and final approval of the version of the article to be published.

**Institutional review board statement:** This research is not a clinical trial and did not require institutional review board approval through The Ohio State University given the de identified nature of this database.

**Conflict-of-interest statement:** All authors declare no conflicts of interest related to this article.

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**Manuscript source:** Unsolicited manuscript

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**Received:** June 2, 2018

**Peer-review started:** June 2, 2018

**First decision:** July 10, 2018

**Revised:** July 23, 2018

**Accepted:** August 21, 2018

**Article in press:**

**Published online:**

**Abstract**

***AIM***

To determine if racial disparities continue to exist in the treatment of hepatocellular carcinoma (HCC).

***METHODS***

A retrospective database analysis using the Nationwide Inpatient Sample was performed including patients with a primary diagnosis of HCC. Univariate and multivariate analyses were utilized to determine racial disparities in liver decompensation, treatment, inpatient mortality, and metastatic disease.

***RESULTS***

A total of 62604 patients with HCC were included consisting of 32428 Caucasian, 9726 African American, 988 Hispanic, and 11462 patients of other races. Caucasian patients are more likely to undergo curative therapies of liver transplant (OR: 2.66, 95%CI: 1.92, 3.68), resection (OR: 1.82, 95%CI: 1.48, 2.23), and ablation (OR: 1.77, 95%CI: 1.36, 2.30) than African American patients. Hispanic patients are more likely to undergo transplant (OR: 2.18, 95%CI: 1.40, 3.39) and ablation (OR: 1.46, 95%CI: 1.05, 2.03) than African American patients. Patients of other races are more likely to receive a liver transplant (OR: 2.41, 95% 1.62, 3.61), resection (OR: 1.79 95%CI: 1.39, 2.32), and ablation (OR: 2.03, 95%CI: 1.47, 2.80) than African American There are no differences in the rates of transarterial chemoembolization between races.

***CONCLUSION***

Racial disparities in HCC treatment exist despite emphasis to support equality in healthcare. African American patients are less likely to undergo curative treatment for HCC.

**Key words:** Racial disparity; Hepatocellular carcinoma; Liver transplantation; Resection; Ablation

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**Core tip:** Racial disparities in the treatment of hepatocellular carcinoma (HCC) have been noted previously. This study investigated continued disparities in healthcare utilizing the Nationwide Inpatient Sample. African American patients were less likely to undergo curative treatment for HCC with liver transplantation, liver resection, ablation and Transarterial Chemoablation despite having less features of liver decompensation. Curative treatment for HCC remains less likely to be performed in African American patients.

Sobotka LA, Hinton A, Conteh LF. African Americans are less likely to receive curative treatment for hepatocellular carcinoma. *World J Hepatol* 2018; In press

**INTRODUCTION**

The incidence of hepatocellular carcinoma (HCC) has increased about 50% since 2003[1,2]. An increasing incidence across all races and ethnic groups has been noted, however the incidence in African American and Hispanic patients has had the largest increase over the past 10 years[1]. The incidence of HCC is two times higher in African American, American Indian, Alaskan Native, and Hispanic patients compared to Caucasian patients[2].Unlike other malignancies such as prostate cancer, where despite increases in incidence, mortality has actually declined, we have seen a concurrent increase in the mortality of HCC as the incidence increases. The mortality rates are twice as high in African American patients compared to Caucasian patients[2,3]. A recent study completed using the Surveillance, Epidemiology and End Results (SEER) database showed the median overall survival of all patients with HCC was 11 months; however, African American patients had a significantly worse prognosis compared to Caucasian patients with only a 9 mo survival rate[4].

Racial disparities in the treatment of HCC have been highlighted in previous studies. African American patients who presented with localized disease were less likely to undergo curative therapy with liver transplantation, surgical resection, and ablation compared to Caucasian patients with the same tumor burden[5,6].Previous studies have also noted that African American patients were more likely to present with metastatic HCC at the time of diagnosis and were therefore no longer candidates for specific curative treatments[7].

This study aims to investigate continued disparities in the treatment of HCC. We hypothesize that racial disparities will continue to be present despite recent emphasis for equal treatment in healthcare.

**MATERIALS AND METHODS**

***Data source***

Utilizing the (Nationwide) Inpatient Sample, which is part of the Healthcare Cost and Utilization Project (HCUP), we performed a retrospective database analysis. The HCUP is one of the largest, publically available inpatient databases. Information obtained include primary and secondary diagnoses and procedures, patient demographics, expected payment source, total charges, discharge status, and length of stay[8]. This study is exempt from review from The Ohio State University Institutional Review Board given patient information is de-identified.

***Study sample***

Utilizing International Classification of Diseases, Ninth Revision, Clinical Modification codes, patient with a primary diagnosis of HCC (ICD-9 155.0) were included in this study. Patients were excluded if they were under the age of 18 or if they had a malignancy in the liver that was not hepatic in origin.

***Outcomes of interest***

Primary outcomes of interest included treatment disparities in HCC based on race which was defined as Caucasian, African American, Hispanic, or other. Specific treatments for HCC that were evaluated included liver transplantation, liver resection, ablation, and transarterial chemoablation (TACE). Secondary outcomes included differences in inpatient mortality, liver decompensation, and metastatic disease.

***Covariates***

Other variables evaluated included gender, age, insurance provider, region where treatment was received, etiology of cirrhosis, features of liver decompensation, metastatic disease, and comorbidities, defined by the Elixhauser Comorbidity (Table 1)[9] . Modification of the Elixhauser Comorbidity score was performed to exclude liver disease. Features of liver decompensation included ascites, jaundice, hepatic encephalopathy and hepatic encephalopathy as previously defined in other studies[10]. These variables were determined by the appropriate ICD-9 code.

***Statistical analysis***

Association between race and factors of interest were evaluated using chi square tests. Multivariate regression models were fit for the presence of metastatic HCC, liver decompensation, mortality, and treatment. Terms in each module were determined through backwards selection where hepatitis C, hepatitis B, alcohol, non-alcoholic steatohepatitis (NASH), primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune liver disease, metastasis, Elixhauser comorbidity score, and treatment were eligible for inclusion where appropriate. Data was analyzed using SAS software (version 9.4).

**RESULTS**

***Demographics***

There were 62582 patients with a primary diagnosis of HCC included in this study. The majority of the patients were Caucasian (32428, 52%) followed by African American (9726, 16%), Hispanic patients (8988, 14%) and patients of other races (8988, 14%).

***Liver Severity, metastatic HCC, and inpatient mortality***

On univariate analysis, features of liver decompensation were significantly different between races (*P* value < 0.001) (Table 1). Multivariate analysis demonstrated that Caucasians and Hispanics patients were more likely to have decompensated liver disease than African American patients [(OR: 1.16, 95%CI: 1.03, 1.30), (OR: 1.28, 95%CI: 1.10, 1.30)] (Table 2).

Univariate analysis concluded the presence of metastatic disease was significantly different between races (*P* value 0.007) (Table 1). On multivariate analysis, Caucasian patients were less likely to have metastatic disease then African American patients with HCC (OR: 0.82, 95%CI: 0.71-0.94). There was no statistical difference between other races (Table 2).

Inpatient mortality was significant between races on univariate analysis (*P* value 0.017) (Table 1). On multivariate analysis, Caucasian patients were less likely to have inpatient mortality compared to African American with HCC (OR: 0.78, 95%CI: 0.65-0.93). There was no statistical difference between other races (Table 2).

***Inpatient treatment of HCC***

There was a significant difference in treatment between races in the univariate analysis (*P* value < 0.001) (Table 1). On stepwise multivariate analysis, Caucasian, Hispanic, and patients of other races were more likely to undergo liver transplantation compared to African American patients [(OR: 2.66, 95%CI: 1.92-3.68), (OR: 2.18, 95%CI: 1.40-3.39), (OR: 2.41, 95% 1.62-3.61)]. Caucasian patients and patients of other races were also more likely to undergo surgical resection than African American patients (OR: 1.82, 95%CI: 1.48-2.23), (OR: 1.79, 95%CI: 1.39-2.32). Caucasian, Hispanic, and patients of other races were more likely to undergo ablation compared to African American patients (OR: 1.77, 95%CI: 1.36-2.30), (OR 1.46, 95%CI: 1.05-2.03), (OR: 2.03, 95%CI: 1.47, 2.80)]. There was no significant difference in the rates of TACE between races (Table 3).

**DISCUSSION**

African American patients are less likely to undergo curative treatment for HCC and this study confirms that treatment disparities continue to exist despite efforts to reduce healthcare disparities. TACE was the only treatment without a disparity in utilization between races. TACE, however, is not considered to be curative for HCC. It is a mean of controlling the malignancy and is often used to downstage tumor burden for liver transplantation or to keep tumor burden within transplant criteria. Differences in treatment exist despite African Americans patients being less likely to present with decompensated disease than Caucasian patients. We know that patients whose disease is better compensated have a better tolerance of liver directed therapies HCC. African American patients have increased rates of metastatic disease and higher inpatient mortality. There are multiple factors that contribute to racial disparities in the management of HCC, including disease progression at time of diagnosis and social determinants of health. It is crucial to recognize these factors and their associations in order to formulate interventions to reduce racial disparities in treatment given the direct effect on patient survival and quality of life.

African American patients are less likely to undergo curative treatment for HCC and many factors influence this disparity, with the presence of metastatic disease being one major limitation to treatment[11]. African American patients were more likely to have metastatic disease at time of initial diagnosis[7]. This may be influenced by decreased HCC screening exams in African American patients[12] and also by genetic differences between races. The presence of metastatic disease is not the only contributor to treatment discrepancies, however. Previous studies have found that African American patients were less likely to undergo surgical treatment for HCC than Caucasian patients even when they presented with the same tumor burden and both group were within Milan criteria[13].

Social factors, specifically the location in which patients receive therapy play a crucial role when considering treatment for patients with HCC. This study showed that the majority of African American patients receive care in the Southern region of the United States and patients living in the Southern United States are less likely to undergo curative therapies of liver transplantation and surgical resection[14,15]. Decreased access to providers who are able to provide timely diagnosis and treatment contributes to this disparity given increased rates of physician and hospital bed inequality in the South compared to North. This makes it more challenging for patients in these areas to access a Hepatologist and a hospital that are better equipped to meet their needs[16].

Racial disparities in the utilization of TACE was not noted in this study, though previous studies have determined a discrepancy in Native Americans and Hispanics compared to Caucasian patients[17]. This intervention may be considered more frequently in African American patients given increased frequency of disease burden outside of Milan criteria. TACE is considered to be a first line treatment for large or multifocal HCC[18] and may be the ideal treatment for many African American patients given initial presentation. However, it should be noted that TACE is not considered curative therapy for HCC. The question of whether it is being offered as the sole treatment option for patients who would otherwise be candidates for curative therapy should be raised. The cost of intervention also influences treatment options. This study shows that African American patients are the largest percentage of patients with Medicaid insurance compared to other races. Previous analysis on cost of intervention for HCC has shown TACE to be one of the least costly interventions[19] and therefore may be the intervention most likely to be reimbursed from government funded insurance.

While it is important to recognize racial disparities in the treatment of patients with HCC, it is crucial to recognize the effect this has on an underrepresented patient’s quality of life and life expectancy. Studies regarding quality of life in patients with chronic liver disease show decreased functional status and increased chronic, debilitating symptoms such as pain, edema, weakness, anorexia, and vomiting compared to patients without any liver disease[20]. These symptoms, specifically bodily pain and fatigue, are worse in patients with liver disease and HCC[21]. Patients with HCC are noted to have higher rates of depression compared to many other malignancies[22], therefore African American patients with HCC that fail to undergo treatment are subject to increased complications and diminished quality of life compared to patients that undergo treatment. Life expectancy is also different between patients that undergo treatment for HCC compared to patients that are not treated[23]. If a patient were to undergo treatment, life expectancy and quality of life are improved[24,25].

Multiple interventions could be utilized to reduce disparities in the treatment of HCC. For example, early recognition of liver disease and risk factors for HCC are key to initiate and continue HCC screening in all patients, but specifically in minority patients that may have reduced access to care. This could potentially lead to earlier diagnosis in patients that may have been preventing later in their disease course and no longer candidate for curative treatment.

Limitations in this study must be noted. This data was obtained through the NIS database through ICD-9 coding. Verification of ICD-9 codes could not be obtained for each patient included in the study given patient privacy restrictions. However, these codes have been verified in previous studies. Other factors that affect the treatment for HCC which are not included in this study, specifically size and number of lesions. Given we are not able to obtain laboratory values, we are unable to determine MELD score, therefore disease severity is defined by features of liver decompensation. Despite limitations, this study has several strengths, the primary being the number of patients that were enrolled in the study and a wide geographic spread. Using the NIS database allowed for the collection of a large number of patients that otherwise would not have been obtained in a single institution study.

Disparities in the treatment of HCC based on patient race continue to exist despite emphasis to decrease disparities in healthcare. Despite having decreased rates of liver decompensation, African American patient have higher rates of inpatient mortality and are less likely to undergo curative treatment with liver transplantation, surgical resection, or ablation. Because these patients are less likely to undergo this intervention, African American patients with HCC are prone to a decreased quality of life and increased mortality rates. Further research needs to be conducted to find ways to decrease this disparity.

**ARTICLE HIGHLIGHTS**

***Research background***

 Rates of hepatocellular carcinoma (HCC) continue to increase. Despite new treatments options, mortality rates are also increasing, specifically in minority patients.

***Research motivation***

Given recent emphasis to minimize health care disparities, we aimed to determine if racial disparities in the treatment of HCC was decreasing.

***Research methods***

We performed a retrospective database analysis utilizing The Nationwide Inpatient Sample including patients with a diagnosis of HCC. Univariate and multivariate analyses were utilized to determine racial disparities in liver decompensation, treatment, inpatient mortality, and metastatic disease.

***Research results***

This large database analysis included 62604 patients with HCC, including 32428 Caucasian, 9726 African American, 988 Hispanic, and 11462 patients of other races. Despite having decreased rates of liver decompensation, African American patient have higher rates of inpatient mortality and are less likely to undergo curative treatment with liver transplantation, surgical resection, or ablation then Caucasian patients.

***Research conclusions***

Racial disparities in HCC treatment exist despite emphasis to support equality in healthcare. African American patients are less likely to undergo curative treatment for HCC.

***Research perspectives***

Further emphasis should be placed on determining why disparities continue to exist and hypothesize ways to reduce in order to facilitate equality in healthcare.

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**P-Reviewer:** Bramhall S, Chiu KW, Kinoshita A, Niu ZS, Tomizawa M **S-Editor:** Cui LJ **L-Editor: E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** United States

**Peer-review report classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): C, C

Grade D (Fair): D

Grade E (Poor): 0

**Table 1 Demographics and clinical parameters in patients with hepatocellular carcinoma grouped by race**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Caucasian****(*n* = 32428)** | **African American****(*n* = 9726)** | **Hispanic****(*n* = 8988)** | **Other****(*n* = 11462)** |  |
|  | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** | ***P* -value** |
| Age (yr) |  |  |  |  |  |  |  |  | < 0.001 |
| ≤ 64 | 17695 | 54.6% | 6980 | 71.8% | 5357 | 59.6% | 6609 | 57.7% |  |
| 65-79 | 10982 | 33.9% | 2287 | 23.5% | 2888 | 32.1% | 3762 | 32.8% |  |
| ≥ 80 | 3751 | 11.6% | 458 | 4.7% | 743 | 8.3% | 1090 | 9.5% |  |
| Gender |  |  |  |  |  |  |  |  | 0.88 |
| Male | 23845 | 73.5% | 7172 | 73.7% | 6572 | 73.1% | 8319 | 72.7% |  |
| Female | 8583 | 26.5% | 2554 | 26.3% | 2416 | 26.9% | 3122 | 27.3% |  |
| Primary payer |  |  |  |  |  |  |  |  | < 0.001 |
|  Medicare | 15765 | 48.9% | 3471 | 35.9% | 3645 | 40.6% | 4520 | 39.5% |  |
|  Medicaid  | 4155 | 12.9% | 2707 | 27.9% | 2206 | 24.5% | 2573 | 22.5% |  |
|  Private Insurance | 9497 | 29.4% | 2236 | 23.1% | 2020 | 22.5% | 3143 | 27.5% |  |
|  Other | 2844 | 8.8% | 1267 | 13.1% | 1118 | 12.4% | 1202 | 10.5% |  |
| Geographic Region |  |  |  |  |  |  |  |  | < 0.001 |
|  Northeast  | 7726 | 23.8% | 2603 | 26.8% | 1829 | 20.4% | 2395 | 20.9% |  |
|  Midwest  | 5904 | 18.2% | 1785 | 18.4% | 536 | 5.9% | 3016 | 26.3% |  |
|  South | 13086 | 40.4% | 4454 | 45.8% | 3126 | 34.8% | 2102 | 18.3% |  |
|  West | 5712 | 17.6% | 883 | 9.1% | 3497 | 38.9% | 3950 | 34.5% |  |
| Discharge year |  |  |  |  |  |  |  |  | 0.917 |
|  2010 | 8180 | 25.2% | 2194 | 22.6% | 2223 | 24.7% | 3162 | 27.6% |  |
|  2011 | 8118 | 25.0% | 2457 | 25.3% | 2386 | 26.5% | 2980 | 26.0% |  |
|  2012 | 7910 | 24.4% | 2490 | 25.6% | 2170 | 24.1% | 2660 | 23.2% |  |
|  2013 | 8220 | 25.4% | 2585 | 26.6% | 2210 | 24.6% | 2660 | 23.2% |  |
| Hepatitis C  | 5056 | 15.6% | 2497 | 25.7% | 1518 | 16.9% | 1737 | 15.2% | < 0.001 |
| Hepatitis B  | 610 | 1.9% | 598 | 6.2% | 236 | 2.6% | 1975 | 17.2% | < 0.001 |
| Alcohol  | 5566 | 17.2% | 1278 | 13.2% | 2023 | 22.5% | 1157 | 10.1% | < 0.001 |
| NASH  | 10802 | 33.3% | 3436 | 35.3% | 3601 | 40.1% | 4140 | 36.1% | < 0.001 |
| Primary Sclerosing Cholangitis  | 326 | 1.0% | 81 | 0.8% | 35 | 0.4% | 140 | 1.2% | 0.046 |
| Primary Biliary Cirrhosis  | 131 | 0.4% | 0 | 0.0% | 10 | 0.1% | 34 | 0.3% | -- |
| Autoimmune  | 91 | 0.3% | 25 | 0.3% | 60 | 0.7% | ≤ 10 | 0.1% | 0.007 |
| Other  | 14336 | 44.2% | 3818 | 39.3% | 2967 | 33.0% | 4566 | 39.9% | < 0.001 |
| Liver Decompensation Features |  |  |  |  |  |  |  |  | < .001 |
|  Zero | 18388 | 56.7% | 5690 | 58.5% | 4475 | 49.8% | 6827 | 59.6% |  |
|  One | 8968 | 27.7% | 2756 | 28.3% | 2846 | 31.7% | 3092 | 27.0% |  |
|  Two | 4074 | 12.6% | 1010 | 10.4% | 1340 | 14.9% | 1242 | 10.8% |  |
|  Three or Greater | 998 | 3.1% | 270 | 2.8% | 328 | 3.6% | 301 | 2.6% |  |
| Metastasis |  |  |  |  |  |  |  |  | 0.007 |
|  None | 27328 | 84.3% | 7841 | 80.6% | 7497 | 83.4% | 9567 | 83.5% |  |
|  Single Site  | 3945 | 12.2% | 1453 | 14.9% | 1092 | 12.2% | 1516 | 13.2% |  |
|  Two or more site  | 1155 | 3.6% | 433 | 4.5% | 399 | 4.4% | 379 | 3.3% |  |
| Elixhauser Comorbidity Score |  |  |  |  |  |  |  |  | < 0.001 |
|  < 3 | 15593 | 48.1% | 4177 | 43.0% | 4255 | 47.3% | 6642 | 57.9% |  |
|  ≥ 3 | 16835 | 51.9% | 5549 | 57.1% | 4733 | 52.7% | 4821 | 42.1% |  |
| Treatment Options |  |  |  |  |  |  |  |  | < 0.001 |
|  Transplant  | 1254 | 3.9% | 190 | 1.9% | 252 | 2.8% | 349 | 3.1% |  |
|  Resection  | 4306 | 13.3% | 823 | 8.5% | 728 | 8.1% | 1644 | 14.3% |  |
|  Ablation | 2031 | 6.3% | 425 | 4.4% | 517 | 5.8% | 833 | 7.3% |  |
|  TACE  | 2419 | 7.5% | 754 | 7.8% | 836 | 9.3% | 939 | 8.2% |  |
|  Noninvasive Treatment | 22418 | 69.1% | 7534 | 77.5% | 6656 | 74.1% | 7697 | 67.2% |  |
| In Hospital Mortality | 2924 | 9.0% | 1120 | 11.5% | 928 | 10.3% | 1151 | 10.1% | 0.017 |

TACE: Transarterial chemoablation; NASH: Non-alcoholic steatohepatitis.

**Table 2 Multivariate logistic regressions comparing outcomes of hepatocellular carcinoma by race**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **Race** | **Adjusted odds ratio** | **95%CI** |
| Metastatic Hepatocellular Carcinoma1 | African-AmericanCaucasianHispanicOther/Unknown | Reference0.820.870.84 | 0.71, 0.940.73, 1.050.70, 1.001 |
| Liver Decompensation2 | African-AmericanCaucasianHispanicOther/Unknown | Reference1.161.281.14 | 1.03, 1.301.10, 1.510.995, 1.31 |
| Inpatient Mortality3 | African-AmericanCaucasianHispanicOther/Unknown | Reference0.780.820.86 | 0.65, 0.930.66, 1.030.69, 1.07 |

1Model is adjusted for age, gender, race, geographic region, hepatitis C, alcohol, non-alcoholic steatohepatitis (NASH), liver decompensation features, and Elixhauser comorbidity score; 2Model is adjusted for age, gender, race, geographic region, hepatitis C, alcohol, NASH, primary biliary cirrhosis, metastasis, and Elixhauser comorbidity score; 3Model is adjusted for age, gender, race, geographic region hepatitis C, hepatitis B, alcohol, NASH, liver decompensation features, metastasis, and treatment.

**Table 3 Multinomial logistic regression to evaluate disparities in treatment for hepatocellular carcinoma based on payer1, 2**

|  |  |  |  |
| --- | --- | --- | --- |
| **Intervention** | **Race** | **Odds ratio** | **Confidence interval** |
| Liver Transplant | African-AmericanCaucasianHispanicOther/Unknown | Reference2.662.182.41 | 1.92, 3.681.40, 3.391.62, 3.61 |
| Resection | African-AmericanCaucasianHispanicOther/Unknown | Reference1.821.241.79 | 1.48, 2.230.94, 1.641.39, 2.32 |
| Ablation | African-AmericanCaucasianHispanicOther/Unknown | Reference1.771.462.03 | 1.36, 2.301.05, 2.031.47, 2.80 |
| TACE | African-AmericanCaucasianHispanicOther/Unknown | Reference1.151.291.19 | 0.93, 1.410.97, 1.720.90, 1.58 |

1Noninvasive treatment is treated as the reference category; 2Model adjusts for age, gender, race, geographic region, hepatitis C, hepatitis B, alcohol, non-alcoholic steatohepatitis, liver decompensation features, and Elixhauser comorbidity score. TACE: Transarterial chemoablation.