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Trends in hepatocellular carcinoma in Louisiana, 2005–2015

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ABSTRACT

Introduction: Louisiana has one of the highest incidence and mortality rates of hepatocellular carcinoma (HCC) in the nation. The aim of this study was to analyze the trends in HCC incidence and relative survival rates in Louisiana and compare them with corresponding national rates, which can be used to formulate strategies to improve Louisiana HCC outcomes.

Methods: Data on primary invasive HCC diagnosed in patients 20 years or older between 2005 and 2015 were obtained from the Surveillance, Epidemiology and End Results (SEER) program and Louisiana Tumor Registry. Time trends in HCC incidence and 12-month relative survival were analyzed using Joinpoint regression. Case characteristics were compared on 2 time periods (2005–2009 and 2010–2015) using Chi-squared tests. Cause-specific survival was analyzed via log-rank and multivariable Cox proportional hazard model.

Results: Over the study period, the average annual percent change (AAPC) in age-adjusted HCC incidence in Louisiana was nearly double that of the national estimate, 6% (95% CI: 4.7, 7.3) compared to 3.1% (95% CI: 2.4, 3.7). 12-month relative survival among HCC patients in Louisiana was 40.7% (95% CI: 38.9, 42.4) which was significantly less than the US rate of 48.2% (95% CI: 47.8, 48.6). Relative survival did improve in Louisiana from 2000 to 2015 at a rate similar to that of the US (AAPC (95% CI): 2.9 (0.7, 5.2) vs. 2.7 (2.3, 3.1), $p = 0.8$). In multivariable survival analysis, factors amongst Louisianans associated with worse survival were older age at diagnosis, advanced stage of disease, and lack of surgical therapy.

Conclusion: The incidence of HCC continues to rise more dramatically in Louisiana than in the US. While some modest improvements in HCC survival have been realized, outcomes remain dismal. Future work identifying the most at-risk populations are needed to inform statewide public health initiatives.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy in the world and the third most common cause of cancer mortality [1]. Although the prevalence is lower in the United States, HCC remains a major public health problem as the incidence of HCC in the US has tripled over the past four decades [2]. Moreover, HCC is one of the most deadly cancers in the US, with a five-year relative survival of only 20% [3–5].

Well-known risk factors for HCC include hepatitis, alcohol abuse, and non-alcoholic fatty liver disease (NAFLD). These risk factors encourage hepatocarcinogenesis by promoting a milieu of chronic hepatic inflammation and/or cirrhosis, and the incidence of HCC varies geographically based on the indigenous incidence of these risk factors [6,7]. Another risk factor associated with liver-related mortality is low socioeconomic status [8]. Louisiana, the bayou state, ranks top 10 in the country in Hepatitis B and Hepatitis C, top 5 in the country in obesity, and number 2 in the nation in the percentage people below the poverty line [9–11]. Louisiana has been ranked in the top 5 states for age-adjusted rate of new liver cancers, and age-adjusted HCC mortality over the past 2 decades [5,7]. Despite this, very little has been written about HCC within the bayou state. In this report, we outline incidence, demographics, treatment patterns, and outcomes of HCC patients diagnosed in Louisiana over an 11-year period with the aim to determine changes over time.

Abbreviations: NS, not significant; HCC, Hepatocellular carcinoma; RS, Relative survival; APC, annual percentage change.

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2. Methods

2.1. Data source and study population

Study data was derived from the 18 population-based registries that are participants of the National Cancer Institute's Surveillance, Epidemiology, and End Results program (SEER 18), which includes registries in the states of Alaska, California, Connecticut, Georgia, Hawaii, Illinois, Iowa, Kentucky, Louisiana, New Mexico, New Jersey, Oregon and Utah [12]. Primary invasive HCC cases diagnosed among those aged 20 and older between 2005 and 2015 were selected using the ICD-O-3 topographic code C220 and histology codes 8170–8180. Cases diagnosed at death or without follow-up duration were excluded. The study was exempted from Institutional Review Board (IRB) approval by the Louisiana State University Health Sciences Center, New Orleans.

2.2. Primary outcomes

The primary outcomes for the study were age-adjusted incidence rates (IR), 12-month relative survival (RS) and cancer-specific survival (CSS) time. Standardized IR and RS were calculated using SEER*Stat software. Relative survival was estimated using the Elderer II method. RS is a net survival measure representing cancer survival in the absence of other causes of death and is measured as the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable set of cancer free individuals [13]. RS adjusts for the general survival of the U.S. population for that socioeconomic status, race, sex, and age. Cases with missing demographic data were excluded from RS analysis. CSS was defined as the number of days from date of initial diagnosis until date of cancer specific death (underlying cause of death is HCC) or date of last contact. All survival analyses were limited to patients with HCC as the only or first primary cancer.

2.3. Case characteristics

Variables pertaining to demographics and patient characteristics were standard North American Association of Central Cancer Registries (NAACCR) items listed in the registry. Liver disease was identified as mild or moderate/severe liver disease using NCI's comorbidity index classification ICD-9 codes listed within the registry [14]. BMI was calculated according to the standard formula (BMI = weight (kilograms) divided by height squared (meters)) when the patient's height and weight was given [15]. BMI was categorized as lean (BMI < 25), overweight ($25 \leq$ BMI < 30), obese ($30 \leq$ BMI < 35) and severely obese (BMI ≥ 35). BMI was listed as a descriptive variable only as the capturing of weight and height data by the LTR only started after 2010 – precluding a comparison between 2005 and 10 and 2010–15. AJCC Stage was issued as either a clinical or a pathologic stage and was merged into one stage for the purpose of analysis, choosing pathologic stage over clinical stage when both staging variables existed and were discrepant. SEER program surgery codes were used to classify liver-directed surgery. Surgery codes were grouped as 00 (none; no surgery of primary site), 10–19 (ablative type procedures), 20–60, 65, 66 (surgical resections) and 61, 75 (transplantation). When code 90 (Surgery, NOS) was encountered, it was attributed to resection for the purpose this analysis. Radiologic arterial-based treatments were not included in this dataset; and therefore were not included as liver directed treatment in this report.

Residential rural-urban status was based on address at time of diagnosis and classified according the US Department of Agriculture Rural Urban Continuum codes [16]. In the state of Louisiana, counties are known as parishes. There were 36 parishes that reported treating at least one patient with HCC during the study period. The top 5 parishes treated at least 225 patients over the study period, which represents the top 15% of parishes in the state. Therefore, the parish case volume was based on the number of HCC patients treated and categorized as low volume (<225) or high volume (>225). Designated Commission on Cancer (COC) facilities in the state were identified by the Louisiana Tumor Registry.

2.4. Statistical analysis

Yearly trends in standardized HCC IR and RS were analyzed using Joinpoint regression. Annual percent change (APC) and average annual percent change (AAPC) were compared between Louisiana and the nationally representative SEER 18 [17]. Additional IR analyses in Louisiana were stratified by race and sex. Louisiana IR trends in races other than Black or African American and white were not reported due to small group numbers.

Next, a detailed comparison of Louisiana cases was completed for two consecutive multiyear periods (2005–2009 and 2010–2015). Changes in demographic, staging, treatment, and outcome coordinate variables between these two periods were analyzed using Chi-squared tests. Cases missing treatment or facility attributes were excluded. Median CSS was estimated using the Kaplan-Meier estimators and compared via log-rank test. Trends and risk factors for CSS were evaluated using a multivariable Cox proportional hazards model. Cases with unknown AJCC stage were excluded from the cox proportional hazards model. Models included age, sex, race, rural residence, liver disease, stage, therapy, parish case volume and facility type were included as fixed effects. A random effect for facility was included to account for clustering of outcomes in patients from the same facility. Categorical comparisons and survival models were executed in SAS/STAT software, version 9.4 (Cary, NC).

3. Results

Time trends in age-adjusted HCC IR for Louisiana and the US are presented as Fig. 1. Over the study period, Louisiana saw a consistent increase in the incidence of HCC from 6.4 to 11.8 per 100,000, for an APC of 6% (95% CI: 4.7, 7.3). The US (SEER 18) also exhibited an increasing HCC incidence, from 7.4 to 9.8 per 100,000, but trend analysis indicated significantly different trends over time when compared to Louisiana (Fig. 1, $p = 0.029$). APC for the US was 4.6% (95% CI: 2.9, 6.3) from 2005 to 2009 but then slowed to 2% (95% CI: 1.3, 2.8) during 2009–2015, with an AAPC of 3.1% (95% CI: 2.4, 3.7).

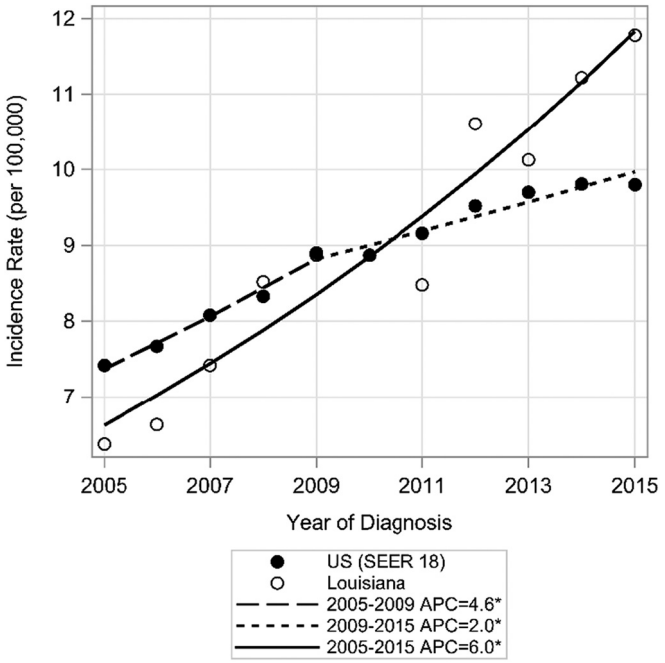

Fig. 1. Trends in age-adjusted incidence of hepatocellular carcinoma, Louisiana 2005–2015. APC = annual percent change. *indicates APC significantly different from zero at alpha = 0.05.

Stratified IR analyses in Louisiana indicated significant increases in HCC in all groups except black women. The largest increase in incidence was seen among black men with an APC of 7.8% (95% CI: 5.5, 10.2), followed by white men (5.4% (95% CI: 3.9, 6.9)), and white women (4.4% (95% CI: 2.1, 6.8)).

Over the full study period, 12-month RS in Louisiana was 40.7% (95% CI: 38.9, 42.4) which was significantly less than the US rate of 48.2% (95% CI: 47.8, 48.6). RS analysis indicated Louisiana patients showed improvement year over year at a rate similar to that of the US (APC (95% CI): 2.9% (0.7, 5.2) vs. 2.7% (2.3, 3.1)) (Fig. 2). The rate of improvement in RS was constant for both Louisiana and the US (SEER 18).

There were 2627 HCC cases in Louisiana eligible for the case-level analysis. Demographic and patient characteristics are outlined in Table 1. Most patients in this dataset were male (81%) and white (57%). 86.7% of cases lived in urban areas. Liver disease diagnoses were observed in 41.2% of cases, with 31.3% having mild liver disease, including alcoholic cirrhosis and chronic hepatitis, and 9.9% having moderate/severe liver disease such as chronic hepatitis with complications, esophageal varices, liver abscesses and other sequelae of chronic liver disease. Of cases with BMI data (n = 1221), 25.9% were classified as obese, with 10.2% having severe obesity.

(BMI ≥ 35). Clinical or pathologic AJCC stage at presentation was unknown in 47.5% of cases. Cases with known stage were relatively evenly distributed across stages I-IV. Despite 29% of cases having documented stage I or II disease, only 23.1% of cases underwent surgical treatment for their HCC. Of patients who did undergo liver-directed surgery, 4% had ablative therapy, 10.5% had resection and 8.6% had liver transplantation. The majority of these cases were treated in COC facilities (84.7%) and in high case-volume parishes (78.7%).

Comparing Louisiana cases over the two periods, there were differences in the distribution of stage at diagnosis and prevalence of liver disease. The rate of unknown AJCC stage decreased from 53.9% in 2005–2009 to 44% in 2010–2015. Of those with known stage, there was a trend towards reduced late-stage disease in the later period, though this was not statistically significant (p = 0.0551). The proportion diagnosed with liver- related comorbidities in the registry significantly increased from 29.1% to 47.8%. However, rates of liver-directed surgery did not differ over the two periods

Table 1
Hepatocellular carcinoma case characteristics, Louisiana 2005–2015.

		Time Period		
	All (n = 2627)	2005–2009 (n = 936)	2010–2015 (n = 1691)	p-value
Age, % (n)				<0.0001
20–49	7.7 (201)	11.2 (105)	5.7 (96)	
50–64	57 (1497)	53 (496)	59.2 (1001)	
65 and older	35.4 (929)	35.8 (335)	35.1 (594)	
Sex, % (n)				0.0042
Female	19 (498)	21.9 (205)	17.3 (293)	
Male	81 (2129)	78.1 (731)	82.7 (1398)	
Race, % (n)				0.4378
White	57 (1497)	58.1 (544)	56.4 (953)	
Black	39.2 (1030)	37.7 (353)	40 (677)	
Other	3.8 (100)	4.2 (39)	3.6 (61)	
Residence, % (n)				0.4504
Urban	86.7 (2277)	86 (805)	87.1 (1472)	
Rural	13.3 (350)	14 (131)	13 (219)	
Liver Disease, % (n)				<0.0001
None	58.9 (1546)	70.8 (663)	52.2 (883)	
Mild	31.3 (821)	20.7 (194)	37.1 (627)	
Moderate or Severe	9.9 (260)	8.4 (79)	10.7 (181)	
AJCC Stage, % (n)				<0.0001
I	18 (473)	15.7 (147)	19.3 (326)	
II	11 (289)	8.3 (78)	12.5 (211)	
III	11.9 (313)	12.4 (116)	11.7 (197)	
IV	11.6 (304)	9.7 (91)	12.6 (213)	
Unknown	47.5 (1248)	53.9 (504)	44 (744)	
Surgical Therapy, % (n)				0.3566
None	76.9 (2021)	77.1 (722)	76.8 (1299)	
Ablative	4 (105)	3.3 (31)	4.4 (74)	
Resection	10.5 (276)	11.4 (107)	10 (169)	
Transplant	8.6 (225)	8.1 (76)	8.8 (149)	
Parish Treatment Volume, % (n)				0.0002
High	78.7 (2068)	76 (711)	80.3 (1357)	
Low	21.3 (559)	24 (225)	19.8 (334)	
Facility Type, % (n)				0.0101
COC	84.7 (2225)	81.2 (760)	86.6 (1465)	
Non-COC	15.3 (402)	18.8 (176)	13.4 (226)	

Abbreviations: AJCC = American Joint Commission on Cancer, COC = Commission on Cancer.

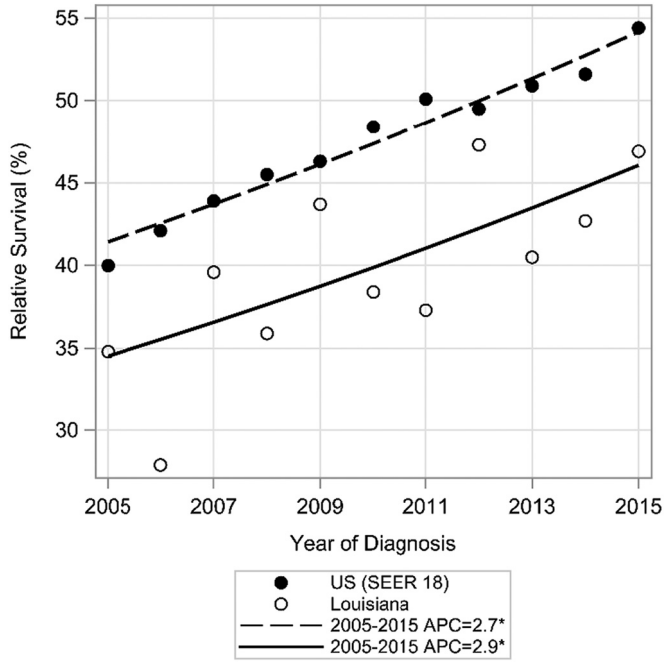

Fig. 2. Trends in 12-month relative survival in cases of hepatocellular carcinoma, Louisiana 2005–2015. APC = annual percent change; * indicates APC significantly different from zero at alpha = 0.05.

(p = 0.3566). The proportion of HCC cases treated in a COC-accredited facility increased from 81.2% in 2005–2009 to 86.6% in 2010–2015 (p = 0.0101). Similarly, the proportion of cases treated in a high case-volume parish increased from 76% to 80.3% (p = 0.0002). Median CSS for patients in the study was 9 months. CSS did improve between the 2 time periods, from 7.1 months to 10.3 (Fig. 3; p = 0.0009).

A total of 1379 patients were included in the multivariable CSS analysis. HCC related death was observed in 70.8% of cases. Patients aged 65 and older had 23% increased rate of death when compared to patients aged 50–64 (HR (95% CI): 1.23 (1.06, 1.42)). Survival was poorer among patients diagnosed with late-stage disease (Stage III HR: 2.34 (1.95, 2.81); Stage IV HR: 3.22 (2.66, 3.9)). All forms of liver directed surgery were associated with improved survival, with 52%, 66%, 88% reduction in the rate of cause specific death for ablation, resection, and transplantation, respectively (Table 2). Risk of death was associated with treatment in a non— COC center (HR; 1.23 (95% CI: 0.94, 1.62)) or in a low-volume parish (HR: 1.12 (95% CI: 0.90, 1.4)) but was not statistically significant.

4. Discussion

The annual incidence of HCC has tripled in the United States since 1975, although recent national data indicate that incidence rates may have plateaued [7,18,19]. Moreover, HCC continues to be a leading cause of cancer related death in the US [4,20]. Well known risk factors for HCC include hepatitis, cirrhosis, diabetes, alcohol consumption, morbid obesity, and NAFLD [21]. These risk factors are all in great abundance in Louisiana.

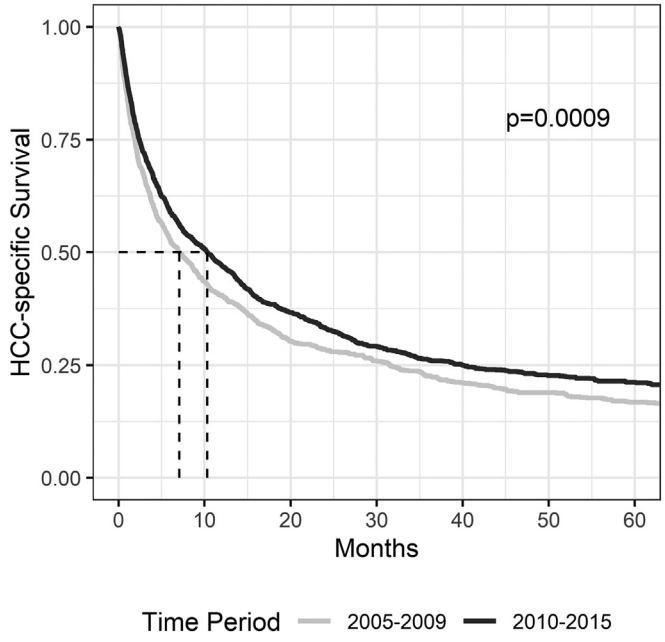

Fig. 3. Kaplan Meier cause-specific survival curves for cases of HCC in Louisiana, 2005–5009 versus 2010–2015. Median survival times are indicated by the dashed lines.

Thus, the bayou state continues to rank in the top 5 states in the nation for HCC incidence and mortality [5,7].

While several studies using SEER and/or US census data have outlined the national trends in HCC incidence and mortality, these studies can mask important patterns that occur at the state level [20–24]. Therefore, we analyzed trends in incidence and survival in Louisiana compared to national data. We also studied state case-level metrics over two periods to assess trends in demographics, treatment patterns, and outcomes to identify areas most in need of improvement.

Table 2
Factors associated with HCC-specific survival from Cox proportional hazards model.

	HR (95% CI)	*p*-value
Age (reference = 50-64)		0.0083
20–49	1.28 (0.98,1.68)	
65 and older	1.23 (1.06,1.42)	
Sex (reference = Female)		0.3642
Male	1.09 (0.91,1.30)	
Race (reference = White)		0.2730
Black	1.11 (0.97,1.27)	
Other	0.94 (0.66,1.33)	
Residence (reference = Urban)		0.9596
Rural	1.01 (0.82,1.23)	
Liver Disease Diagnosis (reference = None)		0.2617
Mild	1.05 (0.91,1.21)	
Moderate or Severe	1.20 (0.96,1.51)	
AJCC Stage (reference = I)		<0.0001
II	1.17 (0.96,1.43)	
III	2.34 (1.95,2.81)	
IV	3.22 (2.66,3.90)	
Surgical Treatment (reference = No)		<0.0001
Ablative	0.48 (0.33,0.70)	
Resection	0.34 (0.28,0.43)	
Transplant	0.12 (0.08,0.17)	
Parish Treatment Volume (reference = High)		0.1965
Low	1.12 (0.90,1.40)	
Facility Type (reference = COC)		0.0959
Non-COC	1.23 (0.94,1.62)	

Abbreviations: HR = hazard ratio, CI = confidence interval, AJCC = American Joint Commission on Cancer, COC = Commission on Cancer.

HCC has long been recognized as a male-dominant disease, and this was similar in Louisiana where over 80% of patients were male [22,24]. While others have disclosed some concerning trends within the Hispanic population, most patients in this study were either white or African American making meaningful analysis of other ethnic groups unfeasible [25]. Of patients with BMI data, 10.2% were severely obese (BMI ≥ 35), and this was slightly less than the 14% obesity rate estimated by Younossi et al. using SEER-Medicare data [26].

Age-adjusted incidence of HCC in Louisiana nearly doubled during the study period. However, unlike other studies that have demonstrated an increase in both men and women of all races, Louisiana's annual percentage increase was mainly in men and in white women, but not in women of color [27]. When we looked at the incidence trend in Louisiana compared to the US, we noted that the US trend started to diminish between 2009 and 2015. By comparison, there was no corresponding diminishment of the incidence rate in Louisiana (Fig. 1). While the plateauing of the national HCC incidence after 2009 has been observed by others using both SEER 18 and the US Cancer Statistics registry [7,18,19,22], White et al. also acknowledged that the national decline was not replicated in some southern states - presumably due to a disproportionately high prevalence of HCC-associated risk factors endemic to them [22]. Our results are consistent with more recent state level analyses, which confirmed that Louisiana experienced consistent increases in HCC incidence during this period [7].

Acknowledging this disparity, the Louisiana Department of Health (LDH), Office of Public Health, LDH Bureau of Health Services Financing (Medicaid), and the Louisiana Department of Corrections (DOC) introduced the Hepatitis C Virus (HCV) Elimination Program in July 2019 [28]. Through an innovative subscription pricing arrangement with Asegua Therapeutics, a subsidiary of Gilead Sciences Inc., this program provides affordable antiviral treatment to HCV-positive Louisiana Medicaid enrollees and incarcerated individuals in DOC facilities. The aim is that 50,000 of the most at-risk, disenfranchised Louisianians will be treated for HCV by 2024; and it is the authors' belief that this will catalyze the slowing of Louisiana's incidence growth to rates equal to or better than that seen nationally.

The median cancer specific survival in Louisiana for HCC during this time period was dismal at 9 months, and the 1-year relative survival was significantly lower than the national rate (40.7% vs. 48.2%). This important finding will be investigated further by this group in the future; but the most obvious and immediate explanation for this difference is the gross underutilization of liver-directed surgery within the bayou state. A 2013 comprehensive meta-analysis of 16 studies and 24,000 HCC patients revealed that such underutilization is a nationwide problem - not unique to Louisiana [29]. However, these authors reported a treatment rate of 58% (range 28–85%) which is more than twice the 23% (median yearly rate 23.2%; Range 17% - 26.2%) rate we observed in Louisiana. One would naturally expect that the underutilization could be explained by advanced stage of disease and/or critical liver-associated comorbidities indigenous to the bayou state. However, this was impossible to assess with any reliability. Firstly, almost half of the patients in this registry (47.5%) had no clinical or pathologic stage documented. Although the AJCC system is less predictive than other HCC models which consider underlying hepatic impairment, the lack of AJCC data illustrates not only a reluctance for practitioners to assign a stage in this disease, but it also leads to a significant limitation in the state registry dataset overall [30]. Secondly, almost 60% of patients had no liver associated comorbidities documented; and of those that did, only 10% were reported as having moderate/severe liver disease. Given our knowledge that 90% of HCC cases develop in a background of cirrhosis, and that this study focused on a state that harbors the top rates of viral hepatitis and gallons of alcohol consumed, we estimate the rate of liver-directed comorbidities to be much greater than what was reported to the registry [9,10,31–33].

This study included all forms of HCC, including HCC combined with cholangiocarcinoma (cHCC-CCA). cHCC-CCA is rare, and while some studies have reported significantly poorer prognosis when compared to HCC alone, others have been inconclusive [34,35]. We feel that the first course

of treatment for cHCC-CCA patients would often be consistent with an HCC diagnosis. And, in order to obtain a representative group, we opted for more inclusive eligibility criteria. However, we do acknowledge that this presents a study limitation. Among the 2627 HCC cases in Louisiana that were included in the study, 25 were cHCC-CCA (less than 1%). We feel that since the inclusion criteria was consistent across comparison groups and the incidence of cHCC-CCA was low overall, excluding these cases would not significantly alter the study conclusions.

There are a few notable positives. The median cancer specific survival increased during the periods of this study. While this increase was only a gain of 3 months, the 1-year relative survival for HCC patients in Louisiana improved by an average of 2.9% per year, and this was similar to the improvement seen nationally (Fig. 3). This finding was associated with a higher percentage of patients that were treated at COC-accredited cancer centers and in higher-volume parishes in the later time-period. Researchers using the Texas state registry also reported a link between improved survival and treatment in higher-volume hospitals, and they attributed this correlation to an increased utilization of liver-directed therapy [36]. While liver-directed surgery was noted to be an independent predictor of survival in Louisiana, its rate did not change between the 2 time periods studied. It is possible, however, that the utilization of non-surgical liver-directed therapy, such as trans-arterial treatments (a metric not captured in the registry), did increase during time studied. This, along with improved selection for these therapies over time, may be responsible for the survival difference observed.

In conclusion, we have uncovered some unsettling data points regarding patients with HCC in Louisiana. Incidence is rising rapidly and faster than the rest of the nation, and it remains worst in men of color illustrating a significant health care disparity that exists along racial and ethnic lines. While outcomes may be modestly improving, HCC survival remains dismal in Louisiana and leaves much room for improvement. Further work will focus on identifying risk factors for treatment underutilization, working to streamline patient care throughout the state to higher volume specialty centers.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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