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DISPARITIES IN TREATMENT OF LIVER LESIONS: NSQIP ANALYSIS OF HOW RACE AFFECTS ONCOLOGIC MANAGEMENT

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Abstract – *Objective:* *Racial disparities are associated with increased healthcare costs and sub-optimal resource utilization. We sought to evaluate racial disparities in the therapeutic management of liver lesions.*

Materials and Methods: *The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database was queried for patients presenting with a liver lesion who had surgical resection (SR) or an ablative procedure (AP). Univariable and multivariable analysis were performed to identify disparities in the treatment rendered. A regression model was constructed to evaluate demographic characteristics favoring AP.*

Results: *Between 2005 and 2016, 8,706 patients were diagnosed with a liver lesion, 7,290 (84%) had SR and 1,416 (16%) had AP. Compared to SR, the AP cohort had a higher number of Native Americans (0.5% vs. 2%; p<0.001), Asians (12.8% vs. 15.5%; p=0.006), African-Americans (9.3% vs. 11.3%; p=0.02), and Hispanics (6.1% vs. 7.7%; p=0.02) but fewer Caucasians (61.7% vs. 55.3%; p<0.001). On multivariable analysis, minority race independently favored AP, with Native Americans demonstrating the highest odds (OR 4.3, 95% CI: 2.3-8.1), followed by Asians (1.3, 95% CI: 1.1-1.6) and African-Americans (1.3, 95% CI: 1.01-1.6).*

Conclusions: *Racial disparities exist in the oncologic management of liver lesions, which could be partly responsible for the lower survival observed among ethnic minorities. These results identify possible opportunities to improve outcomes and healthcare costs associated with the treatment of liver lesions.*

KEYWORDS: *Liver lesion, Tumor, Racial Disparity, NSQIP, Management.*

LIST OF ABBREVIATIONS: *ACS: American College of Surgeons; ACS-NSQIP: American College of Surgeons-National Surgical Quality Improvement Program; AP: Ablative Procedure; BMI: Body Mass Index; CPT: Current Procedural Terminology; HCC: Hepatocellular Carcinoma; HCV: Hepatitis C Virus; ICD: International Classification of Disease; INR: International Normalized Ratio; LL: Liver Lesion; MELD-Na: Model for End-Stage Liver Disease-Sodium; NSQIP: National Surgical Quality Improvement Program; RFA: Radiofrequency Ablation; SGOT: Serum Glutamic-Oxaloacetic Transaminase; SPSS: Statistical Package for the Social Sciences; SR: Surgical Resection; TACE: Transarterial Chemoembolization; WBC: White Blood Cell*

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality worldwide and is one of the leading causes of death in patients with cirrhosis[1]. HCC is the most common type of liver cancer, with approximately 20,000 people diagnosed in the US each year[2]. In the United States, HCC incidence and mortality rates are increasing, although the burden of HCC is not equally distributed throughout the population, with racial minorities having higher incidence rates and mortality[1-4]. The higher incidence of HCC amongst racial and ethnic minorities is thought to be multifactorial, including reversible environmental factors and genetic predispositions[5,6]. Several efforts are underway to reduce the disparity in reversible environmental factors, including public health programs for weight loss management, alcohol abuse, and increasing HCV detection and treatment[7,8].

Recently, national efforts to improve the survival from HCC have focused on well-known racial disparities in the surgical and oncologic management of these patients. Racial disparities are associated with increased readmissions, complications, and mortality, which also lead to inadequate resource utilization and increased overall costs [9].

The optimal therapy for a patient presenting with a liver lesion (LL) is highly dependent on underlying liver disease, anatomic factors, and patient performance status. The treatment of LL is often multidisciplinary, with surgical resection (SR) reserved for patients with minimal liver disease, and regional therapies including trans-arterial chemoembolization (TACE), radiofrequency ablation (RFA), and microwave ablation, reserved for patients with advanced liver disease. The management choice is often also heavily influenced by the presenting stage.

We sought to evaluate racial disparities in the context of therapeutic choice for management of patients presenting with a LL, by using a validated, nationwide, multicenter surgical database. We hypothesized that racial/ethnic minorities would be less likely to receive SR for LL.

MATERIALS AND METHODS

Data source and inclusion criteria

We queried the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) database from 2005 to 2016, for patients who had a SR or an ablative procedure (AP) for the diagnosis of a LL. The ACS-NSQIP is a prospectively-maintained surgical outcomes database that collects pertinent administrative and clinical information during the pre-, intra-, and post-operative period. Case reviewers from participating hospitals abstract information from clinical and administrative records to capture >100 variables in the database for every surgical procedure that is systematically-sampled. Detailed information on ACS-NSQIP participating facilities, sampling methodology, and program implementation can be obtained from the ACS website and previous literature[10, 11].

We utilized Current Procedural Terminology (CPT) codes and International Classification of Disease (ICD- 9 &10) diagnosis codes to identify all those patients who underwent SR (CPT codes: 47120, 47125, 47130, 47122) or AP (CPT Codes: 47380, 47381,47370, 47371) for a malignant neoplasm of the liver (ICD codes 155, 155.0, 155.1, 155.2, C22.0-C22.9). We excluded all those patients who had both SR and AP concurrently.

Data variables

We analyzed demographic variables including age, sex, and race. Race was categorized as American Indian/Alaska Native, Asian, African-American, Hispanic, Caucasian, and other.

Other variables included body mass index, comorbidities such diabetes mellitus, current smoking status, ascites, bleeding disorders, transfusion >4 units packed red blood cells in 72 hours before surgery, preoperative total bilirubin, preoperative aspartate transaminase, preoperative alkaline phosphatase, preoperative white blood cell count, preoperative platelet count, wound classification, and systemic sepsis status.

We analyzed and compared 30-day postoperative complications collected by ACS-NSQIP including mortality, return to operating room, septicemia, bleeding, wound, cardiac, respiratory, renal, and thromboembolic complications.

Statistical analysis

We stratified patients on whether they had SR or AP. We then performed a univariate analysis to compare baseline variables. To identify independent factors associated with an increased propensity to receive AP, we constructed a multivariate logistic regression model. Our dependent variable was the presence of the type of treatment; and as independent covariates we included all variables that had *p*-value <0.1 on univariate analysis. Variable entered into the model: gender, race, diabetes mellitus with oral agents or insulin, current smoker within one year, ascites, bleeding disorders, transfusion >4 units

packed red blood cells in 72 hours before surgery, preoperative total bilirubin, preoperative SGOT, preoperative alkaline phosphatase, preoperative WBC, preoperative platelet count, wound classification, age of patient, BMI, systemic sepsis. We utilized conditional backward selection to determine independent associations. To confirm the validity of our model, we performed appropriate regression diagnostics, including calculating the Hosmer-Lemeshow goodness-of-fit test, testing for outliers, and using classification tables to compare the predicted *vs.* actual outcomes. On univariate analysis, to compare both patient cohorts, we used the χ^2 test and the Fisher's exact test for categorical variables, the Mann-Whitney U test for nonparametric continuous variables, and the independent-samples *t*-test for parametric continuous variables. We utilized a two-sided $\alpha = 0.05$, and all statistical analysis was conducted using SPSS Version 25 (SPSS Inc., IBM, Armonk, NJ, USA).

RESULTS

Between 2005 and 2016, 8,706 patients were captured in the database with a LL; 7,290 (84%) had SR and 1,416 (16%) had AP (Table 1). Compared to the SR cohort, the AP cohort had a higher number of Native Americans (0.5% *vs.* 2%; $p<0.001$), Asians (12.8% *vs.* 15.5%; $p=0.006$), African-Americans (9.3% *vs.* 11.3%; $p=0.02$), and Hispanics (6.1% *vs.* 7.7%; $p=0.02$) but fewer Caucasians (61.7% *vs.* 55.3%; $p<0.001$). There were less women in the SR and AP cohorts compared to males (37.2% *vs.* 62.8%, 26.7% *vs.* 73.3%, respectively; $p<0.001$). The AP cohort had a higher proportion of diabetic patients (29.3 *vs.* 25.3%; $p=0.002$), active smokers (28% *vs.* 21.6%; $p<0.001$), and patients with ascites (6.1% *vs.* 1.7%; $p<0.001$), despite having comparable MELD-Na scores, functional status, and modified frailty index scores between groups.

There was no significant difference in BMI between the two groups (27.9% *vs.* 28%; $p=0.125$). Patients with coagulopathy had higher odds of receiving an AP compared to SR (14.5% *vs.* 4.5%; $p<0.001$). There was no difference in preoperative creatinine values between both groups (0.9 *vs.* 0.9, $p=0.113$). There was no difference in preoperative sodium values between both groups (138.7 *vs.* 138.2; $p=0.125$). The AP group had a higher preoperative bilirubin value (1 *vs.* 1.1; $p<0.001$). The SR group had a higher preoperative platelet count (229.4 *vs.* 140.1; $p<0.001$).

The univariate analysis of post-intervention variables is listed on Table 2. SR had higher operative time than AP (230 min vs 140 min; $p<0.001$) and a longer total length of stay (6.6 days *vs.* 3.6 days; $p<0.001$). The SR cohort also had higher superficial surgical site (4.3% *vs.* 1.3%; $p<0.001$) and organ space infection (8.1% *vs.* 1.6%; $p<0.001$). On univariate comparisons between SR and AP, several postoperative adverse events were associated more likely to be associated with SR, including urinary tract infections, sepsis and septic shock, prolonged intubation, unplanned reintubation, progressive renal insufficiency, acute renal failure, pulmonary embolism, cardiac arrest, deep venous thrombosis. The SR cohort also had a higher rate of blood transfusion, reoperative, and mortality.

On multivariable analysis, minority race was independently associated with receiving an AP, with Native Americans having the highest odds (OR 4.3, 95% CI: 2.3-8.1), followed by Asians (1.3, 95% CI: 1.1-1.6) and African-Americans (1.3, 95% CI: 1.01-1.6) (Table 3). Smokers were more likely to have an AP (1.3, 95% CI: 1.1-1.5). Clinical characteristics favoring an AP included: ascites (2.4, 95% CI: 1.6-3.5) coagulopathy (1.5, 95% CI: 1.3-2.0) an elevated bilirubin, and a lower platelet count.

DISCUSSION

Racial and ethnic disparities in the survival from HCC are thought to be multifactorial[12]. HCC surveillance rates are lower in minorities, thus interventions to increase these rates could be one area of improvement in overall HCC survival in minorities[13]. To gain a better understanding of this phenomenon, we present data that demonstrates disparity trends in the management of LL.

While the mainstay of HCC treatment is SR, the majority of patients are not eligible for this because of tumor extent or underlying liver dysfunction[14]. Our data confirms that patients undergoing AP are more likely to have baseline ascites, elevated INR, and bleeding disorders compared to the SR cohort. While these findings are consistent with previous observations that minority patients are more likely to present with advanced disease, a recent study using the National Cancer Database demonstrated that for early-stage HCC, SR has improved outcomes compared to AP, regardless of tumor size and extent of liver disease[14]. Thus, the findings from our multivariate model confirm that even for patients who present with an advanced LL or with significant liver dysfunction, Caucasian patients are still more likely to have a SR for lesions detected earlier.

Several studies have shown that many patients with HCC do not ultimately receive any HCC treatment, with lower treatment rates amongst ethnic minorities compared to Caucasian patients[16].

TABLE 1. Univariate Analysis: Pre-intervention.

Variable	Hepatectomy (n = 7290)		Ablative Procedures (n = 1,416)	p
Race	*American Indian/Alaska Native*		0.5% (37)	2.0% (29)	<0.001
	Asian		12.8% (933)	15.5% (220)	0.006*
	African American		9.3% (676)	11.3% (160)	0.020*
	Hispanic		6.1% (443)	7.7% (109)	0.024*
	Caucasian		61.7% (4,497)	55.3% (783)	<0.001*
	Other		9.7% (704)	8.1% (115)	0.073
Demographics	*Age*[b]		63.4 ± 12.0	63.3 ± 9.9	0.765
	Gender[a]	Female	37.2% (2,712)	26.7% (378)	<0.001*
		Male	62.8% (4,573)	73.3% (1037)	
	BMI[b]		27.8 ± 5.9	28.0 ± 5.8	0.125
Preoperative Morbidities[a]	*Diabetes*		25.3% (1846)	29.3% (415)	0.002*
	Dyspnea				
		At rest	0.4% (32)	0.7% (10)	0.340
		On moderate exertion	7.6% (553)	8.1% (114)	
	Functional Status				
		Partially dependent	98.9% (7210)	98.7% (1397)	0.427
		Totally dependent	0.2% (11)	0% (0)	0.230
	Mechanical ventilation		0.1% (10)	0% (0)	0.383
	Smoker		21.6% (1,577)	28.0% (397)	< 0.001*
	COPD		5.7% (418)	6.5% (92)	0.266*
	Ascites		1.7% (123)	6.1% (86)	<0.001*
	Congestive heart failure		0.4% (29)	0.4% (6)	0.888
	Pneumonia		0.2% (4)	0.2% (1)	0.941
	Renal disease		0.2% (12)	0.1% (2)	0.841
	Hypertension		58.4% (4,261)	56.9% (806)	0.286
	Cancer		5.7% (413)	4.4% (63)	0.065*
	Open wound		0.8% (56)	0.5% (7)	0.266
	Steroid use		2.9% (214)	3.3% (47)	0.438
	Weight loss		5.6% (405)	2.4% (34)	<0.001*
	Bleeding disorder		4.5% (325)	14.5% (206)	<0.001*
	Blood transfusion		0.7% (49)	0.3% (4)	0.093
	Modified Frailty Index		2 (0,2)	2 (0,4)	0.108
Preoperative Sepsis[a]	*None*		98.2% (7,137)	98.7% (1,394)	< 0.149
	Sepsis		0.3% (21)	0% (0)	
	Septic shock		0.1% (5)	0% (0)	
	SIRS		1.4% (105)	1.3% (18)	
Preoperative Laboratory Values[b]	*Sodium*		138.7 ± 3.1	138.2 ± 3.3	0.125
	BUN		16.1 ± 7.5	15.7 ± 7.9	< 0.001*
	Creatinine		0.9 ± 0.5	0.9 ± 0.6	0.113
	Albumin		3.8 ± 0.6	3.6 ± 0.6	0.113
	Bilirubin		1.0 ± 1.2	1.1 ± 0.9	<0.001*
	SGOT		52.9 ± 1.2	68.5 ± 54.9	<0.001*
	ALP		137.3 ± 120	121.3 ± 67.1	<0.001*
	WBC		7.1 ± 3.9	5.6 ± 2.4	<0.001*
	Hematocrit		39.6 ± 5.2	39.1 ± 5.3	<0.001*
	PTT		30.2 ± 5.2	31.6 ± 6.3	<0.001*
	INR		1.1 ± 0.2	1.1 ± 0.3	<0.001*
Wound Class[a]	*Platelet Count*		229.4 ± 102.5	140.1 ± 76.1	<0.001*
	Clean-I		17.7% (1291)	42.3% (599)	
	Clean/Contaminated-II		76.5% (5578)	55.0% (779)	<0.001*
	Contaminated-III		3.8% 335)	2.0% (29)	
	Infected-IV		1.2% (86)	0.6% (9)	
ASA Score[a]	*1*		0.5% (38)	0.4% (5)	
	2		19.9% (1,453)	13.1% (186)	
	3		71.0% (5,173)	75.7% (1072)	< 0.001*
	4		8.4% (615)	10.7% (151)	
	5		0.1 % (6)	0.1% (1)	

Abbreviations: ACS NSQIP = American College of Surgeons National Surgical Quality Improvement Program, ALP = alkaline phosphatase, ASA = American Society of Anesthesiologists, BMI = body mass index, BUN = blood urea nitrogen, COPD = chronic obstructive pulmonary disease, SGOT = serum glutamic-oxaloacetic transaminase, SIRS = systemic inflammatory response syndrome, WBC = white blood cell count.
*2-tailed $p \leq 0.05$; [a]Categorical variables measured as counts and percentages; [b]Continuous variables as measured by the ACS NSQIP participant user file,values represent mean and standard deviation.

TABLE 2. Univariate Analysis: Post-intervention.

Outcome Variablea	*Hepatectomy (n = 7290)*	*Ablative Procedures (n = 1,416)*	*p-value*
Operative Time(mins)	230.0 ± 106.8	140.1 ± 78.2	<0.001*
Total Length of Hospital Stay (days)	6.6 ± 3.5	3.6 ± 3.6	<0.001*
Postoperative Infectious Complications			
Superficial Surgical Site Infection	4.3% (312)	1.3% (18)	<0.001*
Deep Incisional Infection	0.9% (64)	0.5% (7)	0.142
Organ Space Infection	8.1% (593)	1.6% (23)	<0.001*
Wound Dehiscence	0.9% (66)	0.4% (6)	0.067
Pneumonia	4.4% (320)	2.5% (36)	0.001*
Urinary Tract Infections	3.0% (220)	1.1% (16)	<0.001*
Sepsis	5.6% (408)	2.3% (32)	<0.001*
Septic Shock	3.3% (244)	1.7% (24)	0.001
Postoperative Non-Infectious Complications			
Prolonged Ventilation (>48 hours)	4.7% (340)	2.4% (34)	<0.001*
Unplanned Re-intubation	5.0% (363)	3.0% (42)	0.001
Progressive Renal Insufficiency	1.5% (107)	0.6% (8)	0.006
Acute Renal Failure	2.3% (165)	1.3% (19)	0.026
Pulmonary Embolism	1.4% (100)	0.2% (3)	0.001
Cardiac arrest requiring CPR	1.5% (111)	0.4% (6)	0.001
Myocardial Infarction	0.8% (57)	0.6% (9)	0.166
Stroke with neurological deficit	0.4% (28)	0.3% (4)	0.563
Coma >24 hours	0.4% (28)	0.3% (4)	0.810
DVT requiring therapy	2.5% (185)	1.0% (14)	<0.001*
Blood Transfusion (Intra/Postoperative period)	20.2% (1475)	5.7% (53)	<0.001*
Re-operation	4.6% (333)	2.0% (29)	<0.001*
Mortality	3.1% (274)	2.5% (36)	0.023*

One study using the Surveillance, Epidemiology, and End Results database demonstrated that African-American patients were less likely to receive SR compared to Caucasian patients even when the presentation stage was accounted for[4]. Another study from the Texas Cancer Registry found that African-American and Hispanic patients were less likely to receive any surgical intervention, including SR[17]. Finally a single-institution study from Indiana University found that African-American HHC patients were less likely to undergo treatment and more likely to receive palliative care or hospice [18]. Our analysis of the NSQIP dataset is consistent with these findings, as we show that ethnic minorities tend to preferentially receive AP over SR in a national cohort.

This study is not without limitations. Firstly, the NSQIP database does not contain any regional or institutional identifiers, thus, clustering effects and regional variations cannot be considered in this analysis. Further, racial disparities in healthcare may be attributed to different upstream patient factors, such as education, employment and insurance status, living conditions, and access to healthcare services. Studies have shown that, as the presenting stage of the HCC worsens, delays in management result in worsening outcomes[19,20]. As such, it is important to consider the presenting stage when attempting to qualify the clinical significance of delays in definitive management for HCC. Because the NSQIP database was developed with the intent to guide quality improvement initiatives to enhance surgical outcomes at the individual institutional level, the database does not contain information to reflect socioeconomic status of patients, a factor well-known to affect outcomes in hepatic tumors. The most significant limitation was an inability to ascertain the exact diagnosis of the LL, including information such as size, pathology, and grade, as this data is not collected in NSQIP. Although the severity of the disease may not have been adequately captured, national data suggests that the majority of LL requiring AP or SR are HCC[14]. Inherent to the use of such a database, selection bias must be considered given that not all cases of LL are captured by the NSQIP methodology. Finally, operative details, such as type of ablation, or extent of SR, are unavailable in NSQIP.

Notwithstanding these limitations, we present a comprehensive analysis of racial disparity in LL management. To our knowledge this is the first time that racial disparity in management of hepatic tu-

TABLE 3. Multivariate Analysis.

Variable	*Adjusted OR*	*Adjusted OR (95% CI)*	*p**
Race			
Native American	4.3	2.3 to 8.1	<0.001
Asian	1.3	1.1 to 1.6	0.003
Black	1.3	1.0 to 1.6	0.045
Smoker	1.3	1.1 to 1.5	0.002
Ascites	2.4	1.6 to 3.5	<0.001
Bleeding Disorder	1.5	1.3 to 2.0	<0.001
Pre-op Blood Transfusion	0.1	0.04 to 0.5	0.002
Pre-op Bilirubin	1.1	1.1 to 1.2	<0.001
Pre-op Platelet Count	0.9	0.8 to 0.9	<0.001
Infected Wound Class I	2.3	1.1 to 5.3	0.036

Variable entered into the model: Gender, Race, Diabetes mellitus with oral agents or insulin, Current smoker within one year, Ascites, Bleeding disorders, Transfusion >4 units PRBCs in 72 hours before surgery, Pre-operative total bilirubin, Pre-operative SGOT, Pre-operative alkaline phosphatase, Pre-operative WBC, Pre-operative platelet count, Wound classification, Age of patient, BMI, Systemic sepsis.

Abbreviations: ALP = alkaline phosphatase, BMI = body mass index, BUN = blood urea nitrogen, SGOT = serum glutamic-oxaloacetic transaminase, WBC = white blood cell count, CI = confidence interval, OR = odds ratio, OS = open surgery.
*2-tailed $p \leq 0.05$.

mors is highlighted using a validated, nationwide surgical database. Having an AP could be considered a surrogate marker for advanced presentation of disease in liver cancer. Even after correction for severity of liver disease, racial disparities exist in the oncologic management of liver cancer. Native Americans, African-Americans and Asians appear to disproportionately be treated with AP. Addressing this disparity should be a fundamental effort to improve outcomes from HCC for ethnic minorities.

CONCLUSIONS

Racial disparities exist in the management of hepatic tumors in the United States, with minorities less likely to receive surgical treatment, and more likely to undergo ablative procedures. More research is required to understand the mechanisms driving this disparity in an effort to improve survival as well as to avoid readmissions and their associated costs.

Ethical Committee:

The study was conducted according to the Helsinki Declaration and the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) policy.

Conflict of interest:

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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