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Comparing treatment patterns of hepatocellular carcinoma at academic centers and non-academic centers within the Mountain Region

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ABSTRACT

Background: Our objective is to explore differences in survival and treatment approaches for hepatocellular carcinoma (HCC) between academic centers (ACs) and non-academic centers (NACs), which may contribute to disparities in the Mountain Region (MR).
Methods: Using the National Cancer Database, HCC cases from 2004 to 2015 in the MR were divided into AC and NAC subgroups. Cox-proportional hazard regression and binary logistic regression were performed to analyze survival, compare treatment patterns, and examine the effect of facility type and surgical approach on margin status.
Results: Treatment at ACs, compared to NACs, is associated with improved survival. At ACs, the odds of surgical or systemic treatment were higher. The odds of receiving radiation and positive margins was lower. Overall, the odds of positive margins was higher with laparoscopic compared to open or an unspecified surgical approach; this relationship persisted on subgroup analysis of NACs, but not ACs.
Conclusions: Treatment of HCC at an AC in the MR increases the odds of surgery and improves survival. A laparoscopic approach increases the odds of positive margins, irrespective of center type.

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Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer mortality world-wide and in the United States (US), and the incidence of HCC within the US has been increasing in recent decades.[1–3] The mortality rate for primary liver cancer has also increased at a faster rate than any other cancer.[4,5]in Advancements in diagnostic imaging and screening have led to earlier detection and identification of resectable disease. For localized HCC, the best treatment options remain surgical in nature liver ablation, liver resection, and liver transplantation.[6] Chemoembolization has also been reported to improve survival in select cases of unresectable HCC. However, despite these advancements, overall age-adjusted mortality rates continued to increase from 1992 to 2005.[3] While it has been largely demonstrated that demographic and socioeconomic factors contribute to survival,[6,8] there is minimal literature examining survival differences between facility types, which may have differing approaches to treatment that may affect survival.

Studies have attributed increasing mortality to the under-utilization of potentially curative therapy, and the low rate of surgical intervention.[6–8] The inappropriate allocation of treatment has been suggested to relate to demographics, socioeconomic status, and insurance status. However, the exact mechanism of how these factors contribute to disparities remains unclear.[6] The Mountain Region (MR) of the US (Arizona, Colorado, Idaho, Montana, New Mexico, Nevada, Utah, and Wyoming) is particularly susceptible to the under-utilization of appropriate therapies. National Cancer Institute-Designated Cancer Centers are particularly sparse in this region, with only half of the states having only one cancer center each. These centers tend to have higher volume and more specialization, which are associated with improved outcomes.[9–12]

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Additionally, the significantly lower density of urbanized areas and urban clusters in this region require patients to travel further to the nearest centers for care.[13] There is currently no literature addressing HCC treatment patterns in the MR.

The aim of our study was to examine variations in survival and treatment patterns within the particularly susceptible MR. After controlling for known factors, such as demographics and socioeconomic status, we aimed to uncover other influences that may have contributed to any outcome disparities. Our findings may serve to highlight areas of future investigation for the increasing trends of mortality that have been seen on a national level. We focused our study by initially comparing outcomes and treatment patterns between academic centers (ACs) and non-academic centers (NACs).

Materials and methods

Data source. Data for this study were taken from the National Cancer Database (NCDB) liver Participant User File (PUF) for the years 2004–2015. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. This database captures a significant portion of diagnosed malignancies in the US through a nationwide, facility-based registry. A standardized set of de-identified patient level data and coding definitions is collected from nationally accredited cancer programs, which include patient demographics, cancer staging, tumor histology, treatment, and survival.

Patient cohort. The NCDB liver PUF was queried for all patients living within the MR with HCC. We identified patients with primary liver cancer (International Classification of Diseases for Oncology 3rd edition disease topography code C22), and then selected those patients with HCC, not otherwise specified (malignant behavior code 8170/1). A total of 6500 cases were identified. The following information was collected for all patients: age (years), gender, race (White, black, American Indian/Native American, Asian, National Hawaii/Pacific Islander, other, unknown), ethnicity (Hispanic, non-Hispanic), Charleson/Deyo comorbidity score (0, 1, 2, 3), NCDB analytic stage group (AJCC pathologic stage, clinical stage used if pathologic stage not reported), great circle distance (distance between patient's residence and hospital, in miles), primary payer, and facility type (academic: >500 new cancer diagnoses annually, at least 4 postgraduate training programs; non-academic: no minimum case load, postgraduate training optional). The cohort was then stratified into those treated at ACs (3,006, 46.2%) and NACs (3,494, 53.8%) (Fig. 1). Patients with unknown NCDB staging were excluded from all survival and statistical analysis.

Treatment Approaches, Surgery, and Margin Status. Treatment approaches were grouped and analyzed across four categories. Overall treatment status was defined as those receiving any treatment or being in active surveillance versus those receiving no treatment. Systemic therapy was defined as receiving or being recommended chemotherapy versus no administration or recommendation for chemotherapy. Radiation therapy was defined as receiving any beam radiation versus no beam radiation administered. Surgical treatment was defined as receiving or being recommended any surgical treatment (including local tumor destruction) versus no performance or recommendation of surgery. Among patients receiving surgical treatment, a procedure was performed in 859 cases. The surgical approach for these cases was collected and identified as open or unspecified, robotic assisted, robotic assisted converted to open, laparoscopic, and laparoscopic converted to open. Positive margin status in cases undergoing surgery was defined as those with any macroscopic or microscopic residual tumor. The NCDB definition of margins is "the final status of the surgical margin after resection of the primary tumor" and does not include biopsies.

Survival and Statistical Analysis. To compare survival, Cox-proportional hazard regression analysis was utilized to calculate hazard ratios across multiple covariates. These included age, gender, race, ethnicity, Charleson/Deyo score, NCDB analytic stage group, great circle distance, primary payer, and facility type. Categorical comparisons utilizing Chi-squared tests were used to compare the overall treatment status, systemic therapy, radiation therapy, and surgical approach between patients at NACs and ACs; in the event cell frequencies were small, likelihood ratio statistics are reported. Logistic regression models were developed to compare the odds of treatment or active surveillance, odds of surgical treatment being performed or recommended, odds of systemic treatment being performed or recommended, and odds of radiation treatment; the same set of covariates was used in this model as in the survival analysis. Additionally, logistic regression was also performed to examine the effect of facility type and surgical approach on overall positive margin status. Covariates for this analysis included age, gender, Charleson/Deyo score, NCDB analytic stage group, primary payer, facility type, and surgical approach. A subgroup analysis of positive margin status was repeated within the AC and NAC subgroups. An alpha level of 0.05 was used for all significance tests. The data were analyzed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA).

Transplants and Crossover Patients. Initial overall analyses included transplants because it is important to know if patients are more likely to be evaluated for transplant at specific facility types. However, since certain centers are likely to have a higher proportion of cases that undergo transplant, which would improve that facility's overall survival, we repeated all of the above analyses after excluding all transplant patients. Additionally, patients seen at more than one facility (crossover patients) are likely to introduce bias if there is a specific referral pattern in the crossover from

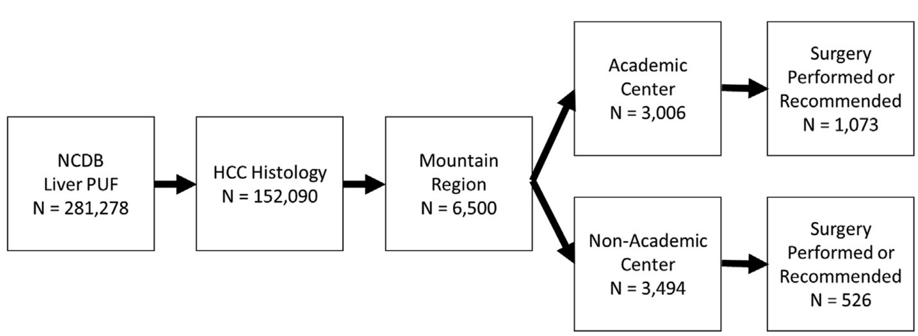

Fig. 1. The NCDB was queried for patients with HCC histology, living within the Mountain Region. This cohort was then divided into those treated at Academic Centers and those treated at Non-Academic Centers. We then performed analyses comparing these groups.

facility to facility. To measure the effect of this bias, we repeated all of the above analyses after excluding all crossover patients.

Results

Demographics. There were significant differences in age, gender, race, ethnicity, Charleson/Deyo Score, NCDB Analytic Stage Group, Great Circle Distance, and Primary Payer between AC and NAC populations (p < 0.01) (Table 1). Demographic variables which were significant were used as model covariates as previously described to control for these differences.

Survival. Intuitively, high Charleson/Deyo scores and high NCDB analytic stage groups were associated with having increased hazards (Table 2). Patients with any insurance were found to have significantly decreased hazard, compared to those not insured (Table 2). We also found that academic centers have decreased hazard compared to non-academic centers (Table 2, Fig. 2).

Treatment Approaches. A greater proportion of patients at ACs than those at NACs received any treatment or were in active surveillance (88.4% vs 75.1%, p < 0.01) (Table 3). The odds of receiving any treatment or being in active surveillance are described in Table 4. The odds at ACs compared to NACs, are lower for American Indian/Native American race compared to white, and higher for Hispanic ethnicity compared to non-Hispanic. The odds of receiving or being recommended surgical treatment or systemic treatment are described in Table 4. At ACs compared to NACs, the odds of surgical treatment and systemic treatment are higher. Compared to white, American Indian/Native American race is associated with a decreased odds of surgical treatment. The odds of receiving radiation is also described in Table 4. At ACs compared to NACs, the odds of radiation treatment was lower. The odds of receiving any treatment or being in active surveillance, receiving or being recommended surgical treatment or systemic treatment, and receiving radiation were higher for nearly all types of insurance (private insurance, Medicaid, Medicare, Other Government) compared to those who were not insured.

Surgical Approach and Positive Margins. A smaller proportion of patients at ACs than those at NACs underwent a laparoscopic approach (22.2% vs 39.9%, p < 0.01) (Table 3). A larger proportion of

Table 1
Patient characteristics.

	Academic	Non-Academic	p-value
Age, mean ± SD	61.27 ± 9.1	65.11 ± 10.7	<0.01
Gender, n, (%)			
Male	2297, (76.4)	2625, (75.1)	0.23
Female	709, (23.6)	869, (24.9)	
Race, n, (%)			
White	2483, (82.6)	3046, (87.3)	<0.01
Black	154, (5.1)	102, (2.9)	
American Indian/Native American	119, (4.0)	106, (3.0)	
Asian	146, (4.9)	143, (4.1)	
National Hawaii/Pacific Islander	14, (0.5)	12, (0.3)	
Other	18, (0.6)	29, (0.8)	
Unknown	72, (2.4)	50, (1.4)	
Ethnicity, n, (%)			
Non-Hispanic	2201, (75.0)	2746, (80.8)	<0.01
Hispanic	732, (25.0)	652, (19.2)	
Charleson/Deyo Score, n, (%)			
0	1696, (56.4)	1637, (46.9)	<0.01
1	621, (20.7)	949, (27.2)	
2	218, (7.3)	351, (10.0)	
3	471, (15.7)	557, (15.9)	
NCDB Analytic Stage Group, n, (%)			
Stage I	1028, (34.2)	852, (24.4)	<0.01
Stage II	711, (23.7)	460, (13.2)	
Stage III	445, (14.8)	720, (20.6)	
Stage IV	307, (10.2)	651, (18.6)	
Unknown	515, (17.1)	808, (23.1)	
Great Circle Distance, n, (%)			
0 miles from facility	128, (4.3)	230, (6.6)	<0.01
1–25 miles from facility	1560, (51.9)	2384, (68.2)	
26–50 miles from facility	246, (8.2)	290, (8.3)	
>50 miles from facility	1072, (35.7)	590, (16.9)	
Primary Payer, n, (%)			
Not Insured	184, (6.1)	195, (5.6)	<0.01
Private Insurance	1135, (37.8)	926, (26.5)	
Medicaid	326, (10.8)	464, (13.3)	
Medicare	1081, (36.0)	1731, (49.5)	
Other Government	205, (6.8)	94, (2.7)	
Unknown	75, (2.5)	84, (2.4)	

Table 2
Cox proportional hazard regression survival analysis.

	Hazard Ratio	95% CI	p-value
Age	1.01	1.01, 1.02	<0.01
Gender:			
Male	–	–	–
Female	0.96	0.89, 1.05	0.36
Race:			
White	–	–	–
Black	0.88	0.74, 1.06	0.18
American Indian/Native American	1.20	0.99, 1.47	0.07
Asian	1.01	0.85, 1.20	0.93
National Hawaii/Pacific Islander	1.35	0.75, 2.45	0.32
Other	0.80	0.46, 1.37	0.41
Unknown	0.57	0.35, 0.93	0.02
Ethnicity:			
Non-Hispanic	–	–	–
Hispanic	1.0	0.92, 1.10	0.97
Charleson/Deyo Score:			
0	–	–	–
1	1.03	0.94, 1.12	0.54
2	1.10	0.97, 1.26	0.15
3	1.14	1.03, 1.26	0.01
NCDB Analytic Stage Group:			
Stage I	–	–	–
Stage II	1.23	1.12, 1.38	<0.01
Stage III	2.70	2.36, 2.87	<0.01
Stage IV	3.88	3.27, 4.02	<0.01
Great Circle Distance:			
0 miles	–	–	–
1–25 miles	0.91	0.78, 1.06	0.21
26–50 miles	0.73	0.60, 0.89	<0.01
>50 miles	0.78	0.66, 0.92	<0.01
Primary Payer:			
Not Insured	–	–	–
Private Insurance	0.43	0.37, 0.50	<0.01
Medicaid	0.60	0.51, 0.71	<0.01
Medicare	0.52	0.44, 0.61	<0.01
Other Government	0.59	0.48, 0.73	<0.01
Unknown	0.45	0.34, 0.59	<0.01
Facility Type:			
Non-Academic	–	–	–
Academic	0.62	0.57, 0.67	<0.01

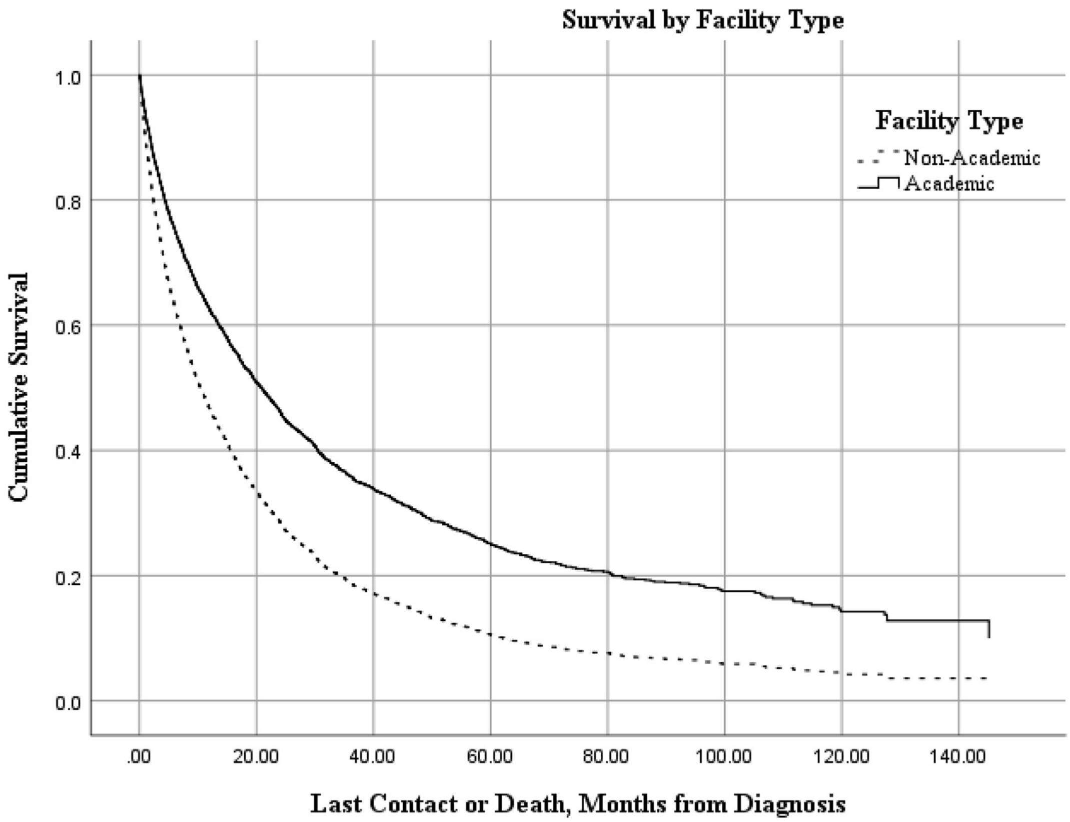

Fig. 2. Survival Curve by Facility Type. Cox proportional hazard regression demonstrates those treated at academic centers had a 0.62 decreased hazard compared to those treated at non-academic centers ($p < 0.01$). This indicates improved long-term survival after controlling for demographic, clinical, and socioeconomic factors.

patients at ACs than those at NACs underwent an open or unspecified approach (75.5% vs 54.2%, $p < 0.01$) (Table 3). After controlling for surgical approach, the odds of positive margins were lower at ACs compared to NACs (Table 5). Overall, the odds of positive margins were higher with a laparoscopic approach compared to open or unspecified (Table 5). On subgroup analysis, the odds of positive margins at ACs were not significantly different between surgical approaches (Table 6). The odds of positive margins at NACs were higher with a laparoscopic approach compared to open or unspecified (Table 6).

Excluding Transplants. A larger proportion of patients do undergo transplant at ACs compared to NACs (19.7% vs 3.4%, $p < 0.01$) (Table 3). After excluding all transplant patients and repeating the analyses, the same patterns persisted. Patients at ACs had a

Table 3
Systemic, radiation, and surgical treatment.

	Academic	Non-Academic	*p*
Treatment Status, n, (%)			
No Treatment Given	193 (11.6)	454 (24.9)	<0.01
Treatment Given or in Active Surveillance	1476 (88.4)	1825 (75.1)	
Systemic Treatment, n, (%)			
No Chemotherapy	949 (38.2)	1413 (53.7)	<0.01
Chemotherapy Administered or Recommended	1533 (61.8)	1217 (46.3)	
Radiation Treatment, n, (%)			
No Radiation	2297 (93.3)	2240 (85.0)	<0.01
Radiation Administered	166 (6.7)	394 (15.0)	
Transplants, n, (%)			
No Transplant	2001 (80.3)	2593 (96.6)	<0.01
Transplant Performed	490 (19.7)	90 (3.4)	
Surgical Approach, n, (%)			
Open or unspecified	422 (75.5)	137 (54.2)	<0.01
Robotic Assisted	4 (0.7)	7 (2.8)	
Robotic Converted to Open	1 (0.2)	0 (0.0)	
Laparoscopic	124 (22.2)	101 (39.9)	
Laparoscopic Converted to Open	8 (1.4)	8 (3.2)	

Table 4
Odds of treatment or active surveillance and specific treatments.

	OR Treatment/Surveillance	*p*	OR Surgical	*p*	OR Systemic	*p*	OR Radiation	*p*
Age	0.99	<0.01	0.98	<0.01	0.99	0.04	1.00	0.68
Gender:								
Male	–	–			–	–	–	–
Female	1.04	0.70	1.20	0.02	0.88	0.07	0.93	0.49
Race:								
White	–	–	–	–	–	–	–	–
Black	0.98	0.94	0.95	0.77	0.89	0.45	1.26	0.32
American Indian/Native American	0.61	0.04	0.58	<0.01	0.93	0.63	0.87	0.60
Asian	1.08	0.74	0.81	0.23	1.31	0.06	0.59	0.06
National Hawaii/Pacific Islander	0.48	0.23	1.00	1.00	0.47	0.12	0.96	0.96
Other	1.15	0.79	0.93	0.86	1.41	0.33	0.82	0.75
Unknown	1.75	0.32	0.86	0.77	0.86	0.67	1.95	0.16
Ethnicity:								
Non-Hispanic	–	–	–	–	–	–	–	–
Hispanic	1.30	0.04	0.75	<0.01	1.23	<0.01	0.85	0.20
Charleson/Deyo Score:								
0	–	–	–	–	–	–	–	–
1	1.20	0.13	0.99	0.86	1.12	0.12	0.95	0.63
2	1.26	0.19	0.95	0.69	1.19	0.10	0.78	0.15
3	0.82	0.11	1.13	0.20	0.84	0.04	0.70	0.02
NCDB Analytic Stage Group:								
Stage I	–	–	–	–	–	–	–	–
Stage II	1.08	0.58	0.89	0.14	1.23	<0.01	1.03	0.85
Stage III	0.64	<0.01	0.31	<0.01	1.33	<0.01	1.37	0.01
Stage IV	0.40	<0.01	0.07	<0.01	1.05	0.55	1.94	<0.01
Great Circle Distance:								
0 miles from facility	–	–	–	–	–	–	–	–
1–25 miles	0.91	0.69	1.33	0.13	0.87	0.29	1.23	0.38
26–50 miles	1.44	0.19	1.96	<0.01	0.82	0.24	1.80	0.03
>50 miles	1.64	0.04	1.70	<0.01	0.95	0.71	1.46	0.12
Primary Payer:								
Not Insured	–	–	–	–	–	–	–	–
Private Insurance	3.37	<0.01	4.09	<0.01	1.64	<0.01	5.46	<0.01
Medicaid	1.84	<0.01	1.50	0.10	1.76	<0.01	3.37	<0.01
Medicare	2.63	<0.01	3.06	<0.01	1.65	<0.01	4.87	<0.01
Other Government	3.24	<0.01	2.12	<0.01	2.34	<0.01	7.82	<0.01
Unknown	2.35	0.02	3.58	<0.01	1.76	0.02	2.52	0.09
Facility Type:								
Non-Academic	–	–	–	–	–	–	–	–
Academic	1.91	<0.01	2.04	<0.01	1.82	<0.01	0.42	<0.01

decreased hazard compared to NACs (HR 0.73, $p < 0.01$). Patients at ACs had increased odds of receiving treatment or being in active surveillance (OR 1.86, $p < 0.01$), increased odds of surgical treatment (OR 1.37, $p < 0.01$), increased odds of systemic treatment (OR 1.74, $p < 0.01$), and decreased odds of radiation treatment (OR 0.53, $p < 0.01$).

Excluding Crossover Patients. Overall, there were 724 patients (11.1%) that had more than one facility report their information to the NCDB. These were likely crossover patients who initially presented to one facility and were referred to another. After excluding all crossover patients and repeating the analyses, the same patterns persisted. Patients at ACs had a decreased hazard compared to NACs (HR 0.59, $p < 0.01$). Patients at ACs had increased odds of receiving treatment or being in active surveillance (OR 1.93, $p < 0.01$), increased odds of surgical treatment (OR 2.10, $p < 0.01$), increased odds of systemic treatment (OR 1.85, $p < 0.01$), and decreased odds of radiation treatment (OR 0.47, $p < 0.01$).

Discussion

The increasing mortality associated with HCC is concerning, and there has been much interest placed on the relationship of demographics and socioeconomic factors on survival.[6,7,14,15] The prevailing sentiment is that these factors predispose a patient to an underutilization of appropriate treatment options, particularly surgical therapy. Surgical resection or transplantation remains as the most effective treatments for HCC in the early stages. Studies have suggested that demographic and socioeconomic factors influence the treatment patterns that patients are likely to receive. Previous studies have shown that patients of black race were more likely to receive no treatment, and patients of Asian race were more likely to receive local and surgical therapy.[2,8] However, these studies relied on Medicare datasets that may not reflect wider conditions in the community. Other studies suggest that patients with Medicare, Medicaid, or no insurance were less likely to have

Table 5
Overall odds of positive margins.

	Odds Ratio	95% CI	p-value
Age	0.98	0.94, 1.03	0.43
Gender:			
Male	–	–	–
Female	1.18	0.56, 2.48	0.66
Charleson/Deyo Score:			
0	–	–	–
1	1.40	0.65, 3.03	0.39
2	0.46	0.12, 1.79	0.26
3	0.18	0.04, 0.72	0.02
NCDB Analytic Stage Group:			
Stage I	–	–	–
Stage II	2.32	0.99, 5.41	0.05
Stage III	13.17	5.64, 30.76	<0.01
Stage IV	13.96	2.24, 87.12	<0.01
Primary Payer:			
Not Insured	–	–	–
Private Insurance	0.36	0.08, 1.65	0.19
Medicaid	0.73	0.13, 4.25	0.73
Medicare	0.87	0.16, 4.09	0.86
Other Government	1.55	0.21, 11.40	0.67
Unknown	<0.01	<0.01	1.0
Surgical Approach:			
Open or unspecified	–	–	–
Robotic assisted	5.89	0.71, 48.61	0.10
Robotic assisted converted to open	0	0	1.00
Laparoscopic	3.46	1.49, 6.50	<0.01
Laparoscopic converted to open	0	0	1.00
Facility Type:			
Non-Academic	–	–	–
Academic	0.24	0.12, 0.49	<0.01

surgery.[7] Additionally, patients in lower socioeconomic classes are more likely to have these types of insurance. The use of the NCDB allows a more accurate analysis of treatment patterns seen throughout the nation. Although AC and NAC cohorts were found to be different, the large sample size of the NCDB allows for robust regression analyses to control for these differences.

In this study of the Mountain Region, after controlling for facility type, insurance, and distance, several disparities in race and ethnicity were identified. American Indian/Native American race is associated with decreased odds of receiving treatment or being in active surveillance and surgical treatment being performed or recommended. This finding could be related to residential patterns for American Indian/Native Americans in the MR. With a larger number of reservations, which tend to be more remote from specialized centers of care, patients are less likely to travel the extended distances necessary to be treated at these centers. We also identified that Hispanic ethnicity was associated with a higher odds of receiving treatment or being in active surveillance and systemic treatment, but lower odds of surgical treatment. None of these disparities in treatment patterns however translated to a decrease in overall survival. Complex cultural beliefs and tendencies may be contributing[16] and further research is indicated to investigate the reason these inequalities persist. Efforts should be made to ensure all early stage patients with HCC have access to surgical treatment.

This study again demonstrates the significant impact that insurance status has on healthcare outcomes. Compared to the uninsured, patients with any type of insurance had significantly greater odds of receiving any treatment. In particular, patients with private insurance had the greatest odds of receiving surgical therapy. Predictably, patients with any insurance, and particularly those with private insurance, had significantly improved survival. Patients in lower socioeconomic classes tend to be either uninsured or take part in Medicare and Medicaid. These findings are useful in understanding the effect that changes to healthcare coverage may have on patients in the future.

While disparities due to socioeconomic, demographic, and insurance status have been well described, another area of focus has been the facility the patient is treated at. After controlling for the above factors, it has been demonstrated that patients seen at small and medium sized hospitals are more likely to receive no therapy, while academic centers are far more likely to perform surgery.[7,8] Hospital type has been shown to affect treatment decisions as well.[17,18] As the actual point of contact and treatment for patients, the facility type may ultimately be the most important factor in the appropriate allocation of treatment. In our analysis, survival was found to significantly differ between patients treated at academic centers and those treated at non-academic centers. Those treated at academic centers had a decreased hazard on multivariate Cox regression.

In order to explore the underlying reasons that may explain this disparity, the treatment approaches between academic centers and non-academic centers were further analyzed and found to be quite different. Patients seen at academic centers were more likely to be given treatment or be in active surveillance. They were also more likely to be recommended or receive chemotherapy, less likely to receive radiation, and more likely to receive or recommended surgical treatment. These findings were observed after controlling for demographic, geographic, and insurance status through multivariate regression. Surgical therapy has consistently been found to be the most effective treatment[6] while chemotherapy[19–21] and radiation therapy[22–24] have been seen as bridge therapy or palliative in nature. Patients treated at academic centers are more likely to receive treatment that is more effective in nature. The nature of HCC may require a more complex multi-disciplinary approach that may not be attainable in some facilities. While more research is indicated to understand why this disparity in treatment approaches exists, improving patient access to academic centers may be a beneficial initial step towards improving outcomes.

Among the patients that received surgical treatment, patients at academic centers were less likely to undergo a laparoscopic approach and less likely to have positive margins. On further analysis, after controlling for demographic, clinical, pathologic, and facility factors, a laparoscopic approach was found to have a higher odds of positive margins compared to open and unspecified. There is literature that suggests laparoscopic resections for HCC have improved perioperative recovery with equivalent oncologic outcomes.[25–31] However, these studies are limited in their scope as they are largely single center experiences from specialized, high-volume academic centers with no randomization and may be affected by reporting bias. In our subgroup analysis, a laparoscopic approach at academic centers was not found to have a significantly higher odds of positive margins. Conversely, a laparoscopic approach at non-academic centers was found to have a significantly higher odds of positive margins. While further research in warranted to explore the relationship of positive margin status on survival, it appears that patients treated at academic centers not only receive the more effective treatment option, but the actual treatment itself is more effective. These disparities in perioperative oncologic outcomes may be the result of a facility's case volume, which has been shown to be particularly important for HCC.[7] Understanding a facility's limitations and referring these patients to facilities that are better equipped may be a necessary step in closing the gap in survival.

Table 6
Academic center versus community odds of positive margins.

	Academic OR	*p*	Community OR	*p*
Age	1.04	0.29	.094	0.06
Gender:				
Male	–	–	–	–
Female	1.87	0.28	0.77	0.66
Charleson/Deyo Score:				
0	–	–	–	–
1	0.91	0.88	2.15	0.16
2	<0.01	1.0	0.86	0.85
3	<0.01	1.0	0.24	0.08
NCDB Analytic Stage Group:				
Stage I	–	–	–	–
Stage II	3.19	0.09	1.70	0.39
Stage III	12.06	<0.01	19.61	<0.01
Stage IV	83.11	<0.01	2.93	0.36
Primary Payer:				
Not Insured	–	–	–	–
Private Insurance	0.48	0.49	0.24	0.30
Medicaid	1.07	0.96	0.64	0.76
Medicare	0.62	0.67	1.07	0.96
Other Government	2.57	0.48	0.48	0.68
Unknown	<0.01	1.0	<0.01	1.0
Surgical Approach:				
Open or unspecified	–	–	–	–
Robotic assisted	16.04	0.05	3.45	0.44
Robotic assisted converted to open	<0.01	1.00	–	–
Laparoscopic	3.38	0.07	4.20	0.01
Laparoscopic converted to open	<0.01	1.0	<0.01	1.0

Transplant and crossover patients were included in the initial overall analysis because it was important to capture actual treatment and referral patterns that are inherent to a facility type when making comparisons about facilities. However, we do understand that this can introduce bias if certain treatments, such as transplants, skew significantly in a certain direction and have a profound survival benefit compared to other treatments. Similarly, patients seen at more than one facility were likely referred to a facility for reasons such as co-morbidities, staging, or access to treatments. If there is a specific pattern to these referrals, this can also introduce bias. To account for these potential biases, we repeated all survival and treatment patterns analyses after excluding transplant patients and after excluding crossover patients. On both analyses, the same patterns persisted, demonstrating that patients seen at ACs continued to have improved survival and were more likely to receive the most effective forms of treatments.

The use of the NCDB to analyze national and regional trends carries several advantages. It is a robust dataset that captures a large proportion of the population of all insurance types. Much of the current literature utilizes SEER-Medicare data which is limited to patients with Medicare and unlikely to be representative of the larger population. The NCDB is also the largest oncologic database that contains detailed information on demographics, socioeconomic factors, clinical parameters, treatment approaches, and outcomes. It is able to capture data on nearly 80% of all cancer patients in the United States, which is the most robust cancer database available. With the ability to capture wider community data, it is not bound by the limitations and potential biases of single-center studies. The collation of wide-ranging information into a large database mitigates reporting bias of narrower focused studies.

Limitations to any studies utilizing the NCDB include those which are associated with using a retrospective database. There is a level of inherent reporting error from the facilities to databases. Correlation can be inferred through the analyses, but causation cannot be concluded. The NCDB is limited it its ability to capture patient preference in the treatment plans that are ultimately carried out. However, this was mitigated by focusing on whether certain treatment options were recommended, but not necessarily performed. There were small sample sizes in particular cohorts, such as robotic assisted surgical approaches. However, these limitations were mitigated by focusing our conclusions on factors that only had adequate sample size. The treatment option of transarterial chemoembolization has been shown to have survival benefits and a role in treatment for HCC.[32] However, the NCDB was unable to specifically capture this treatment option. A treatment like this would be captured by the NCDB as an 'Other Treatment' and in our analysis, only 1.1% of patients overall received 'Other Treatment'. This small of a percentage would unlikely change the significance of our findings. Another limitation is that we are unable to determine the number of cirrhotic patients in our cohort. The MELD score is unfortunately not captured in the NCDB, and the variables needed to calculate it are also not included. Instead, the Charlson-Deyo score is utilized by the NCDB to assess comorbidities. While cirrhosis is included in Charlson-Deyo score, and there is likely an association between a higher Charlson-Deyo score and higher MELD score, we are unable to determine which patients got a point for cirrhosis.

Conclusion

After controlling for socioeconomic and demographic factors, treatment of HCC at an academic center is associated with improved survival. Further analysis demonstrates this may be associated with a superior allocation of treatment options, particularly surgery. When surgery is performed, patients at academic centers have improved perioperative oncologic outcomes, including margin status. A laparoscopic approach has been independently shown to increase the odds of positive margins. This relationship persisted in subgroup analysis of non-academic centers, but not academic centers. While further research is needed to determine whether these outcomes are causative in improving survival, efforts should be made to improve patient access to academic centers in the Mountain Region.

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Declaration of competing interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.09.025.

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