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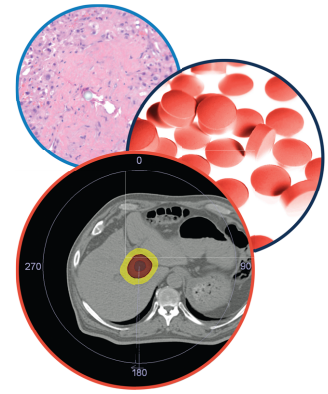

Hepatic Oncology

Locoregional therapy patterns and healthcare economic burden of patients with hepatocellular carcinoma in the USA

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Aim: To examine the locoregional therapy (LRT) patterns and the healthcare economic burden of patients with hepatocellular carcinoma (HCC) in the USA. **Patients & methods:** Patients with newly diagnosed HCC were identified from the MarketScan® databases (1 July 2015–31 May 2018). The LRTs received and all-cause and HCC-related healthcare costs were measured. **Results:** Among 2101 patients with HCC, most received embolization therapy as their first LRT treatment (57.8%, n = 1215); 17.1% (n = 360) received ablative therapy and 8.7% (n = 182) radiation therapy; 16.4% (n = 344) received multiple LRTs. After patients received their first LRT treatment, total all-cause healthcare costs averaged $20,316 per patient per month; 70.7% ($14,359) were HCC related. **Conclusion:** Among newly diagnosed HCC patients treated with LRT in the USA, the economic burden is high.

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Keywords: healthcare economic burden • hepatocellular carcinoma • locoregional therapies • treatment patterns

Hepatocellular carcinoma (HCC) is the primary malignancy of the liver, accounting for up to 90% of all liver cancer cases [1]. Globally and in the USA, the incidence of HCC has been increasing; worldwide, 80% of HCC cases are associated with chronic hepatitis C (HCV) or hepatitis B viral infections, which are also key drivers of the USA's increase in HCC cases [2–4]. Diabetes, obesity, nonalcoholic fatty liver disease and alcoholic liver disease are also associated with a greater risk of developing HCC, primarily resulting from progressive liver cirrhosis [4].

With 5-year survival rates of up to 70%, surgical resection and liver transplantation are considered the most curative treatments for HCC [5]. However, these surgical procedures are only feasible for patients with early-stage HCC who meet certain criteria, which represents only 20–30% of those diagnosed with HCC [6]. Many patients are not diagnosed with HCC until they have reached intermediate- or advanced-stage disease [5,6]. For those who are not candidates for surgical intervention, locoregional therapies (LRTs), including ablative therapy, embolization therapy (transarterial embolization [TAE], transarterial chemoembolization [TACE], transarterial radioembolization [TARE]) and radiation therapy are treatment options [5,6]. Embolization therapy is a common treatment choice for patients with intermediate-stage HCC, while ablative therapy is more often used for early-stage disease [5,6]. For those patients with advanced-stage HCC, the most commonly used systemic therapy has been the multi-kinase inhibitor, sorafenib, which in clinical trial settings has demonstrated a modest clinical benefit in the extension of overall survival [5,6]. However, with the recently published favorable overall survival and progression-free outcomes of patients with advanced HCC treated with atezolizumab plus bevazicumab versus sorafenib, this immunotherapy combination treatment option is likely to become more widespread in use among patients diagnosed with advanced HCC [7]. Other systemic treatment options with a survival benefit and currently recommended by the American Association for the Study of Liver Diseases and European Association for the Study of the Liver for the treatment of advanced stage HCC include lenvatinib, regorafenib and cabozantinib; more general treatment recommendations are given for newer systemic treatment options (e.g., ramucirumab, nivolumab, pembrolizumab) [1,8].

Future Medicine

Although there are several studies in which the treatment patterns and/or healthcare costs of patients diagnosed with any stage or advanced stages of HCC have been evaluated in real-world settings [3,9–15], there is limited information available regarding the real-world treatment patterns and healthcare economic burden specifically of patients diagnosed with locoregional disease, especially in USA. In the multi-national BRIDGE Study, Park *et al.* reported that TACE, which was the most commonly used first-line therapy across patients with any stage HCC, was received by a third of patients in North America 2005–2012 (n = 2326; 37% had stage 0-A; 10% had stage B; 53% had stage C or D) [3]. In a multi-center Italian study, TAE/TACE was received by 63% of patients diagnosed with intermediate stage disease, while 1% received TARE as their first-line therapy [13]. In a study of Medicare patients (1992–2005), those with localized disease (n = 2182) averaged $7265 in medical costs per patient per month (PPPM; 2009 USD); the treatments received were not reported [14]. In another study of Medicare patients (2000–2007) diagnosed with any stage of HCC, but who were all treated with TACE, cumulative Medicare expenditures were estimated at between $74,788 and $148,878 (2011 USD), depending on how many TACE procedures were received [15]. To gain a better understanding of more contemporary treatment patterns and healthcare costs of patients treated with LRTs in the USA, in this study we conducted a retrospective observational analysis using administrative healthcare claims data to examine the real-world LRTs received, LRT treatment characteristics, and the healthcare economic burden of patients with newly diagnosed HCC during the period from 1 July 2015 through 31 May 2018 in the USA.

Materials & methods

Study design & data sources

This study was a retrospective observational analysis that used administrative healthcare claims from the IBM® MarketScan® Commercial and Medicare Supplemental databases. These databases are comprised of individual level, de-identified, healthcare claims from people located in all ten US census regions. Used primarily for research, these databases are fully Health Insurance Portability and Accountability Act (HIPAA) compliant and capture patient-level inpatient medical, outpatient medical and outpatient pharmacy services, in addition to total and patient out-of-pocket (OOP) payments and health plan enrollment.

Study population

Patients (≥18 years of age) with newly diagnosed HCC during the period from 1 July 2015 through 31 May 2018 (index identification period) and who received ≥1 LRT after diagnosis (1 January 2016–31 May 2018) were identified from the MarketScan databases. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) diagnosis code of 155.0 or the ICD-10 codes, C22.0 and C22.8, were used to indicate HCC. LRTs were identified by Current Procedural Terminology, Healthcare Common Procedure Coding System, ICD-9 and ICD-10 procedure codes for ablative therapy, embolization therapy (TAE/TACE or TARE procedures), and radiation therapy. The date of the earliest locoregional procedure during the index identification period was designated as the index date. Patients were required to have 6 months of continuous health insurance enrollment prior to the index date (baseline period) and ≥1 month after (follow-up period). The follow-up period was censored when patients initiated any systemic therapy since we were interested in understanding the patient journey during LRT. Patients were excluded from the study population if they met any of the following exclusion criteria: had any other primary cancers or metastases during anytime of the entire study period; had liver cancer or a liver transplant during the baseline period; had any evidence of pregnancy during anytime of the entire study period; had locoregional or systemic therapy during the baseline period; and participated in a clinical trial during anytime of the entire study period. Also, patients with any prior HCC diagnoses in the 6 months before the earliest HCC diagnosis to occur during the index identification period were excluded to select for newly diagnosed HCC patients. The patient selection process is described in Figure 1. The eligible overall study population was additionally stratified into cohorts according to the first type of LRT patients received (ablative therapy, embolization therapy, radiation therapy or multiple LRTs).

Patient demographic & clinical characteristics

During the 6-month baseline period or on the index date, patient demographic data, including age, gender, US geographic region of residence and health plan type, and clinical characteristics, including Charlson Comorbidity Index score (without cancer included in the score) and key comorbid conditions were evaluated.

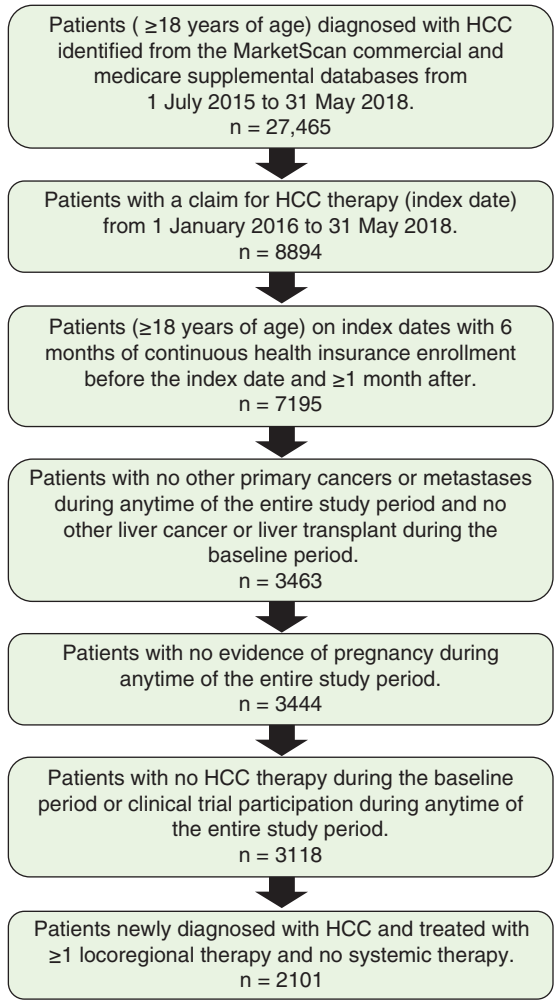

Figure 1. Patient selection process.
HCC: Hepatocellular carcinoma.

LRT treatment patterns

During the variable follow-up period of ≥1 month, LRT treatment characteristics were evaluated for the overall study population and study cohorts stratified by the type of the first LRT received. For patients, the first LRT treatment began on their index date; subsequent second and third LRT treatments began on the date of the first LRT procedure to occur after the end of the previous LRT treatment. An LRT treatment was defined as all treatments received within the first 28 days after the start of the LRT treatment. The end of an LRT treatment was designated by a new treatment or treatment discontinuation (i.e., a therapy coverage gap of >90 days from the end of the current therapy coverage duration to the beginning of the next therapy), whichever was earlier. The duration of treatment was defined as 1 day for locoregional procedures. The evaluated LRT treatment characteristics included the count and proportions of patients who received a first, second and third LRT treatment, the durations of each LRT treatment, the durations between LRT treatments, the durations from index dates to the start of each LRT treatment, and the LRTs received. For TAE/TACE and TARE, the number of procedures received was also reported.

Healthcare cost outcomes

During the variable follow-up period of ≥1 month, all-cause and HCC-related healthcare costs (total paid payments and patient OOP payments) were also measured for the overall study population and study cohorts stratified by the type of first LRT received. Total all-cause healthcare costs, with a breakdown of inpatient medical service

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cost, outpatient medical service cost and outpatient pharmacy cost, and total HCC-related healthcare costs, with a breakdown of inpatient medical service cost and outpatient medical service cost, were reported PPPM in 2019 USD.

Statistical analyses

Bivariate descriptive statistics were utilized to test for statistically significant differences in patient demographic and clinical characteristics, LRT treatment characteristics and healthcare costs between patient cohorts. Categorical variables were presented as the count and percentage of patients in each category, and continuous variables were summarized by mean, median and standard deviation (SD). T-tests and chi-square tests were used to detect statistically significant differences in continuous and categorical variables. A critical value of 0.05 was used to determine statistical significance. All statistical analyses were carried out using SAS® 9.4.

Results

Demographic & clinical characteristics of overall study population & study cohorts

Demographic and clinical characteristics of the overall study population and study cohorts stratified by the type of the first LRT treatment received are shown in Table 1. Among the 2101 patients with newly diagnosed HCC who received ≥1 LRT treatment, mean age was 63.9 years (median: 63 years) and 75.0% were male. The mean follow-up duration was 11.5 months. Across age groups, HCC was most prevalent among those 55 to 64 years of age (52.4%). Among the overall study population in their first LRT treatment, most received embolization therapy (57.8%, n = 1215); 17.1% (n = 360) received ablative therapy and 8.7% (n = 182) radiation therapy; 16.4% (n = 344) received multiple LRTs (the most common combination therapies were radiation/TARE [33.4%], radiation/TAE/TARE [25.9%] and radiofrequency microwave ablation/TAE [20.9%]).

Patients who received radiation therapy as their first LRT treatment were older (mean age: 65.8 years), with 17.0% ≥80 years of age, compared with 5.8% to 7.3% in this age group in the other study cohorts. General comorbidity level, as measured by Charlson Comorbidity Index score, was a mean of 3.7 among the overall study population and it did not statistically significantly differ across the study cohorts. The comorbid conditions with the highest prevalence among the overall study population included cardiovascular disease (84.1%), liver cirrhosis (77.4%), bleeding (69.3%), hypertension (62.7%), chronic HCV infection (48.7%) and diabetes (40.5%) (Table 2). Among those who received radiation therapy, the prevalence of cirrhosis (50.0%) and chronic HCV (29.1%) was lower than in the other study cohorts (Table 2).

LRT treatment patterns

Among the overall study population, 72.2% received only 1 LRT treatment during the follow-up for a mean duration of 29 days; 20.1% received a second LRT treatment for a mean duration of 18.5 days, and 7.7% received a third LRT treatment for a mean duration of 9.8 days (Table 3).

A majority of patients received embolization therapy at any time of the follow-up periods (77.3%; n = 1623), with 68.7% (n = 1443) having received TAE/TACE and 20.7% (n = 434) TARE; 27.3% (n = 574) received ablative therapy and 28.1% (n = 590) received radiation therapy; 30.9% (n = 649) of patients received multiple LRTs (Table 3). Among those who received TAE/TACE, 59.4% had 1 procedure, 32.1% had 2–3 procedures, and 8.5% had 4 or more procedures. Among those who received TARE, 74.9% had 1 procedure, 24.7% had 2–3 procedures and 0.5% had 4 or more procedures (Table 3).

Healthcare cost outcomes

Among the overall study population during the follow-up, total all-cause healthcare costs were a mean of $20,316 (OOP: $378) PPPM, of which 70.7% ($14,359; OOP: $227 PPPM) were HCC related (Figure 2). Total costs and the breakdown of all-cause and HCC-related healthcare costs are shown for the overall study population and the study cohorts in Table 4. Total all-cause ($30,417 PPPM) and HCC-related ($24,564 PPPM) healthcare costs were highest among those who received multiple LRTs in their first LRT treatment. Among patients who received 1 LRT in their first treatment, total all-cause healthcare costs were lowest for those who received ablative therapy ($11,401 PPPM); they were generally similar for those who received embolization therapy ($20,010 PPPM) and radiation therapy ($20,901 PPPM). HCC-related healthcare costs were also lowest for patients who received ablative therapy ($6,111 PPPM); they were $14,332 PPPM for those who received embolization therapy and $11,565 PPPM for those who received radiation therapy. Outpatient medical service costs generally contributed the most to total

Table 1. Demographics and clinical characteristics of the overall study population and study cohorts stratified by the type of the first locoregional therapy received.

Characteristic	Overall study population (n = 2101)	Ablative therapy (n = 360)	Embolization therapy (n = 1215)	Radiation therapy (n = 182)	Multiple LRTs (n = 344)	p-value
Age (years), mean (SD)	63.9 (9.4)	63.4 (9.2)	63.4 (9.2)	65.8 (11.9)	64.9 (8.6)	0.001
Age group, n (%)						0.001
18–34	12 (0.6)	5 (1.4)	7 (0.6)	0 (0.0)	0 (0.0)	
35–44	32 (1.5)	4 (1.1)	17 (1.4)	9 (5.0)	2 (0.6)	
45–54	183 (8.7)	29 (8.1)	114 (9.4)	14 (7.7)	26 (7.6)	
55–64	1101 (52.4)	199 (55.3)	649 (53.4)	78 (42.9)	175 (50.9)	
65–69	282 (13.4)	46 (12.8)	166 (13.7)	17 (9.3)	53 (15.4)	
70–74	198 (9.4)	34 (9.4)	110 (9.1)	17 (9.3)	37 (10.8)	
75–79	140 (6.7)	22 (6.1)	76 (6.3)	16 (8.8)	26 (7.6)	
≥80	153 (7.3)	21 (5.8)	76 (6.3)	31 (17.0)	25 (7.3)	
Gender, n (%)						0.001
Male	1576 (75.0)	259 (71.9)	925 (76.1)	118 (64.8)	274 (79.7)	
Female	525 (25.0)	101 (28.1)	290 (23.9)	64 (35.2)	70 (20.4)	
US geographic region, n (%)						< 0.001
South	770 (36.7)	117 (32.5)	476 (39.2)	50 (27.5)	127 (36.9)	
North Central	485 (23.1)	104 (28.9)	233 (19.2)	71 (39.0)	77 (22.4)	
Northeast	450 (21.4)	67 (18.6)	249 (20.5)	39 (21.4)	95 (27.6)	
West	396 (18.9)	72 (20.0)	257 (21.2)	22 (12.1)	45 (13.1)	
Health plan type, n (%)						0.068
PPO	1066 (50.7)	178 (49.4)	632 (52.0)	84 (46.2)	172 (50.0)	
Comprehensive	347 (16.5)	61 (16.9)	191 (15.7)	43 (23.6)	52 (15.1)	
HMO	256 (12.2)	47 (13.1)	146 (12.0)	18 (9.9)	45 (13.1)	
POS	177 (8.4)	26 (7.2)	110 (9.1)	8 (4.4)	33 (9.6)	
CDHP	108 (5.1)	20 (5.6)	65 (5.4)	12 (6.6)	11 (3.2)	
Other types	147 (7.0)	28 (7.8)	71 (5.8)	17 (9.3)	31 (9.0)	
CCI score (without cancer), mean (SD)	3.7 (2.2)	3.7 (2.1)	3.8 (2.2)	3.4 (2.2)	3.7 (2.2)	0.081
CCI score group (without cancer), n (%)						0.005
0	26 (1.2)	1 (0.3)	11 (0.9)	8 (4.4)	6 (1.7)	
1–2	730 (34.8)	130 (36.1)	407 (33.5)	71 (39.0)	122 (35.5)	
3–4	553 (26.3)	98 (27.2)	321 (26.4)	45 (24.7)	89 (25.9)	
≥5	792 (37.7)	131 (36.4)	476 (39.2)	58 (31.9)	127 (36.9)	
Follow-up duration (months), mean (SD)	11.5 (11.2)	13.3 (11.4)	11.9 (11.6)	7.4 (8.3)	10.2 (10.0)	< 0.001

p-values are for the comparisons across all study cohorts.
CCI: Charlson comorbidity index; CDHP: Consumer driven health plan; HMO: Health maintenance organization; LRT: Locoregional therapy; POS: Point of service; PPO: Preferred provider organization; SD: Standard deviation.

all-cause and HCC-related healthcare costs, although they were lowest for those who received ablative therapy as their first treatment.

Discussion

Currently, there is limited published information about the real-world treatment patterns and healthcare economic burden of newly diagnosed HCC patients who receive LRT. This is one of the first large-scale studies using a nationally representative healthcare claims database to examine the real-world LRTs received, LRT treatment characteristics, and the healthcare economic burden of patients with newly diagnosed HCC in the USA. The overall study population included 2101 patients with newly diagnosed HCC treated with LRT. Some patient characteristics of this study population differed to some degree from those of the North American study population

Table 2. Prevalence of comorbid conditions among the overall study population and study cohorts stratified by the type of the first locoregional therapy received.

Comorbid condition, n (%)	Overall study population (n = 2101)	Ablative therapy (n = 360)	Embolization therapy (n = 1215)	Radiation therapy (n = 182)	Multiple LRTs (n = 344)	p-value
Liver related						
Liver cirrhosis	1627 (77.4)	310 (86.1)	973 (80.1)	91 (50.0)	253 (73.6)	< 0.001
Chronic HCV infection	1024 (48.7)	188 (52.2)	622 (51.2)	53 (29.1)	161 (46.8)	< 0.001
Portal hypertension	682 (32.5)	126 (35.0)	419 (34.5)	37 (20.3)	100 (29.1)	0.001
Chronic hepatitis	300 (14.3)	62 (17.2)	167 (13.7)	23 (12.6)	48 (14.0)	0.353
Alcoholic cirrhosis	209 (10.0)	43 (11.9)	119 (9.8)	11 (6.0)	36 (10.5)	0.184
Chronic HBV infection	144 (6.9)	26 (7.2)	94 (7.7)	3 (1.7)	21 (6.1)	0.022
Liver fibrosis	119 (5.7)	18 (5.0)	77 (6.3)	6 (3.3)	18 (5.2)	0.340
Nonalcoholic fatty liver	100 (4.8)	22 (6.1)	53 (4.4)	6 (3.3)	19 (5.5)	0.365
Nonalcoholic steatohepatitis	97 (4.6)	20 (5.6)	53 (4.4)	6 (3.3)	18 (5.2)	0.590
Hemochromatosis	55 (2.6)	6 (1.7)	33 (2.7)	5 (2.8)	11 (3.2)	0.617
Alcoholic hepatitis	22 (1.1)	5 (1.4)	11 (0.9)	2 (1.1)	4 (1.2)	0.875
Alcoholic fatty liver	14 (0.7)	3 (0.8)	9 (0.7)	1 (0.6)	1 (0.3)	0.795
Alpha-1-antitrypsin deficiency	7 (0.3)	1 (0.3)	5 (0.4)	0 (0.0)	1 (0.3)	0.829
Wilson's disease	4 (0.2)	0 (0.0)	0 (0.0)	1 (0.6)	3 (0.9)	0.005
Cardiovascular and metabolic related						
Overall cardiovascular disease	1766 (84.1)	289 (80.3)	1017 (83.7)	158 (86.8)	302 (87.8)	0.036
Hypertension	1317 (62.7)	213 (59.2)	746 (61.4)	121 (66.5)	237 (68.9)	0.023
Congestive heart failure	154 (7.3)	16 (4.4)	92 (7.6)	20 (11.0)	26 (7.6)	0.043
Diabetes	851 (40.5)	135 (37.5)	499 (41.1)	65 (35.7)	152 (44.2)	0.159
Obesity	268 (12.8)	41 (11.4)	162 (13.3)	20 (11.0)	45 (13.1)	0.680
Metabolic syndrome	6 (0.3)	2 (0.6)	4 (0.3)	0 (0.0)	0 (0.0)	0.474
Bleeding related						
Bleeding	1456 (69.3)	278 (77.2)	840 (69.1)	115 (63.2)	223 (64.8)	0.001
Esophageal varices with bleeding	95 (4.5)	20 (5.6)	60 (4.9)	4 (2.2)	11 (3.2)	0.168
Esophageal varices without bleeding	522 (24.9)	85 (23.6)	331 (27.2)	28 (15.4)	78 (22.7)	0.003
Proteinuria	29 (1.4)	5 (1.4)	12 (1.0)	3 (1.7)	9 (2.6)	0.149

p-values are for the comparisons across all study cohorts.
HBV: Hepatitis B virus; HCV: Hepatitis C virus; LRT: Locoregional therapy.

in the BRIDGE Study, including mean age (64 vs 62 years), percentage male, (75 vs 77%) and most notably, the prevalence of HCV infection (49 vs 39%) [3]. In our study population, approximately 7% had chronic hepatitis B virus infection, liver cirrhosis affected 77% and concomitant cardiovascular disease was widespread, occurring in 84% of the study population; 41% had diabetes. Generally, the patient characteristics, including HCC risk factors and prevalence of comorbid conditions, of our study population are within the ranges of those reported from a multitude of other US studies of patients diagnosed with any stage of HCC included in a systematic literature review [16]. The patient data described herein provides a better understanding of the general patient characteristics and comorbidity level of the patient population with newly diagnosed HCC and treated with LRT.

Among our study population identified with a new HCC diagnosis during the period from 1 July 2015 through 31 May 2018, nearly three quarters only received 1 LRT treatment during the follow-up, which averaged almost 1 year. Most (77.3%) received embolization therapy, which was predominately TAE/TACE versus TARE; 28% received radiation therapy, which was more frequently used for patients who were 80 years of age and older than

Table 3. Locoregional therapy treatment characteristics of the overall study population and study cohorts during the follow-up.

LRT treatment characteristics	Overall study population	Ablative therapy	Embolization therapy	Radiation therapy	Multiple LRTs	p-value
LRT treatments						< 0.001
First LRT treatment, n (%)	1517 (72.2)	293 (81.4)	844 (69.5)	157 (86.3)	223 (64.8)	
Duration (days), mean (SD)	15.3 (28.6)	3.1 (10.7)	18.3 (34.9)	22.4 (17.4)	13.5 (13.8)	< 0.001
Second LRT treatment, n (%)	423 (20.1)	49 (13.6)	268 (22.1)	17 (9.3)	89 (25.9)	
Days from index to initiation of second treatment	188.5 (173.2)	296.6 (208.9)	182.5 (158.2)	153.6 (158.4)	154.1 (177.6)	< 0.001
End of first treatment to initiation of second treatment (days), mean (SD)	169.6 (174.3)	293.2 (210.1)	160.0 (156.9)	132.0 (156.5)	138.3 (179.9)	< 0.001
Duration (days), mean (SD)	8.2 (18.5)	7.9 (15.4)	8.2 (19.7)	9.7 (19.7)	8.1 (16.2)	0.980
Third LRT treatment, n (%)	161 (7.7)	18 (5.0)	103 (8.5)	8 (4.4)	32 (9.3)	
Days from index to initiation of third treatment	373.9 (231.8)	481.7 (251.1)	383.2 (236.2)	268.1 (162.0)	310.0 (197.7)	0.041
End of second treatment to initiation of third treatment (days), mean (SD)	169.2 (147.5)	160.0 (181.0)	180.4 (157.4)	168.1 (138.5)	138.6 (84.1)	0.569
Duration (days), mean (SD)	9.8 (18.5)	6.4 (13.4)	10.0 (20.3)	19.8 (17.2)	8.6 (14.2)	0.384
Type of therapy received at any time during the follow-up						
Embolization therapy, n (%)	1623 (77.3)	44 (12.2)	1215 (100)	21 (11.5)	343 (99.7)	
TAE including TACE	1443 (68.7)	38 (10.6)	1144 (94.2)	13 (7.1)	248 (72.1)	< 0.001
Number of TAE/TACE procedures						0.004
1 procedure	857 (59.4)	26 (68.4)	652 (57.0)	7 (53.9)	172 (69.4)	
2–3 procedures	463 (32.1)	11 (29.0)	381 (33.3)	6 (46.2)	65 (26.2)	
4+ procedures	123 (8.5)	1 (2.6)	111 (9.7)	0 (0)	11 (4.4)	
TARE	434 (20.7)	10 (2.8)	188 (15.5)	11 (6.0)	225 (65.4)	< 0.001
Number of TARE procedures						0.989
1 procedure	325 (74.9)	8 (80.0)	144 (76.6)	8 (72.7)	165 (73.3)	
2–3 procedures	107 (24.7)	2 (20.0)	43 (22.9)	3 (27.3)	59 (26.2)	
4+ procedures	2 (0.5)	0 (0)	1 (0.5)	0 (0)	1 (0.4)	
Ablative therapy, n (%)	574 (27.3)	360 (100)	116 (9.6)	4 (2.2)	94 (27.3)	
Radiation therapy, n (%)	590 (28.1)	16 (4.4)	121 (10.0)	182 (100)	271 (78.8)	
Multiple LRTs, n (%)	649 (30.9)	51 (14.2)	229 (18.9)	25 (13.7)	344 (100)	

p-values are for the comparisons across all study cohorts.
LRT: Locoregional therapy; SD: Standard deviation; TACE: Transarterial chemoembolization; TAE: Transarterial embolization; TARE: Transarterial radioembolization.

the other LRTs; 27% received ablative therapy. Among the North American population and among all patients with stage B disease in the BRIDGE Study, TACE was also the most commonly used first LRT [3]. In our study, 31% of patients received multiple types of LRTs during the follow-up, of which there is evidence for providing more favorable outcomes versus a single type of therapy based on meta-analyses of clinical trial data [17,18]. The majority (59%) of patients who received TAE/TACE only received 1 procedure in the follow-up, despite evidence

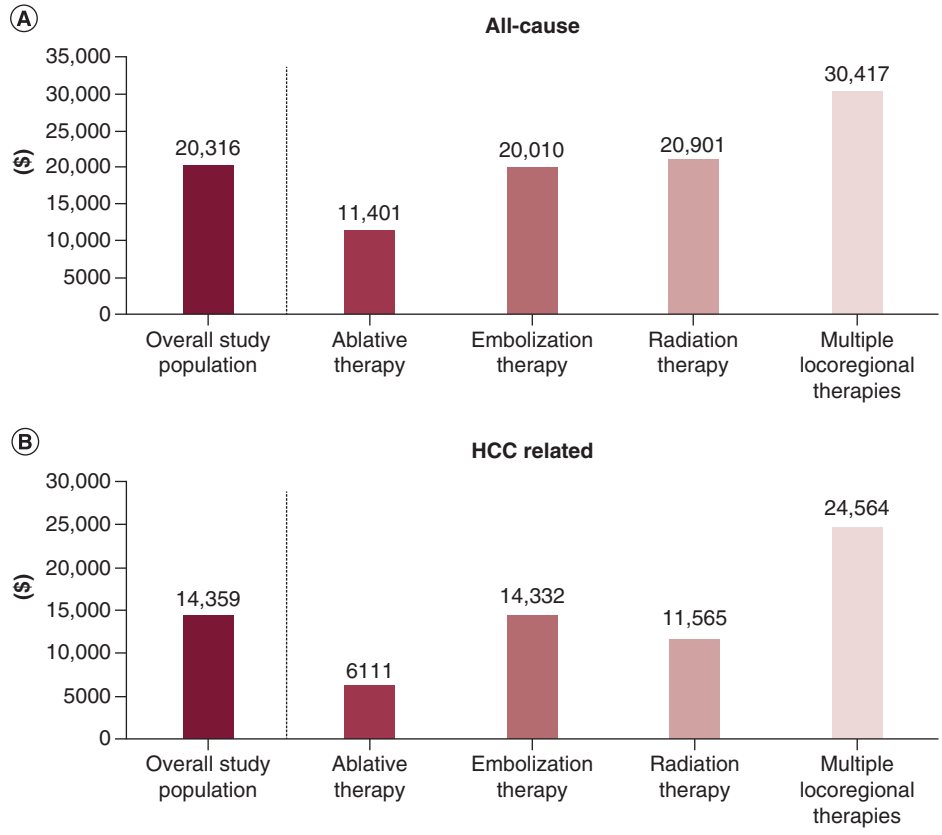

Figure 2. All-cause total healthcare costs (A) and hepatocellular carcinoma-related total medical costs (B) of the overall study population and study cohorts during the follow-up per patient per month. All cost data are reported as means in 2019 USD. $p < 0.001$ for the comparisons of all-cause and HCC-related costs across the study cohorts.
HCC: Hepatocellular carcinoma; PPPM: Per patient per month.

Table 4. Breakdown of healthcare costs of the overall study population and study cohorts during the follow-up per patient per month.

Healthcare resource category	Overall study population	Ablative therapy	Embolization therapy	Radiation therapy	Multiple LRTs	p-value
All-cause						
Total healthcare cost	$20,316 ($26,447)	$11,401 ($13,762)	$20,010 ($21,208)	$20,901 ($31,023)	$30,417 ($42,402)	< 0.001
Total patient OOP cost	$378 ($691)	$287 ($476)	$380 ($643)	$390 ($789)	$457 ($937)	0.013
Inpatient medical service cost	$5675 ($19,489)	$4359 ($10,146)	$5944 ($14,271)	$7090 ($25,283)	$5357 ($34,003)	0.404
Outpatient medical service cost	$12,762 ($17,820)	$4930 ($6823)	$12,118 ($15,257)	$12,936 ($17,742)	$23,142 ($27,046)	< 0.001
Outpatient pharmacy cost	$1878 ($5425)	$2112 ($5519)	$1948 ($5714)	$875 ($3957)	$1919 ($4884)	0.068
HCC related						
Total medical cost	$14,359 ($23,064)	$6111 ($9121)	$14,332 ($18,037)	$11,565 ($15,938)	$24,564 ($41,283)	< 0.001
Total HCC-related patient OOP medical cost	$227 ($565)	$136 ($294)	$228 ($503)	$213 ($641)	$324 ($855)	< 0.001
Inpatient medical service cost	$4160 ($16,966)	$3204 ($8196)	$4657 ($12,146)	$2542 ($8068)	$4260 ($33,650)	0.278
Outpatient medical service cost	$10,199 ($16,455)	$2908 ($4141)	$9674 ($14,068)	$9023 ($13,987)	$20,304 ($26,005)	< 0.001

All cost data are reported as means with standard deviations in 2019 USD. p-values are for the comparisons across all study cohorts.
HCC: Hepatocellular carcinoma; LRT: Locoregional therapy; OOP: Out of pocket; PPPM: Per patient per month.

showing that most patients do not achieve a complete response with only 1 procedure [18]. TAE/TACE was the most common LRT treatment also for patients who had second and third LRT treatments.

During the follow-up, total all-cause healthcare costs averaged $20,316 PPPM, of which 71% ($14,359 PPPM) were HCC related. All-cause healthcare costs PPPM were higher among patients who received radiation therapy ($20,901 PPPM) and embolization therapy ($20,010 PPPM) than among those who received ablative therapy ($11,401 PPPM); they were very sizeable among those who received multiple LRTs as their first treatment ($30,417 PPPM). Patients who received embolization therapy had the highest HCC-related costs. Outpatient medical service costs contributed the most to the total all-cause and HCC-related healthcare costs of patients treated with embolization therapy, radiation therapy and multiple LRTs, all of which can be performed in outpatient settings. However, these types of procedures can also involve a brief inpatient stay. Ablative therapy, primarily a nonsurgical treatment not involving radioactivity that can also be performed in the outpatient setting, was associated with less outpatient medical service costs than the other LRTs.

Patients diagnosed with HCC and treated with locoregional therapies have relatively high healthcare costs relative to patients with other types of nonmetastatic cancers. An administrative US commercial/Medicare Advantage claims-based study of patients with nonmetastatic colorectal, lung or breast cancer reported mean annual all-cause healthcare costs of $150,674 ($12,556 PPPM), $118,495 ($9,875 PPPM) and $78,560 ($6,547 PPPM) (2014 USD) [19]. The high all-cause healthcare costs of patients newly diagnosed with HCC are likely related to their disease stage at diagnosis, the costly treatments and other medical services they receive, and also their high prevalence of comorbidities, including cardiovascular disease and cirrhosis. Earlier diagnosis, involving guideline-recommended disease surveillance of those at high risk of progressing to HCC, antiviral therapy when appropriate, in addition to better surveillance after diagnosis and initial treatment for prevention of HCC progression/recurrence [1,8], may help reduce the healthcare economic burden of patients newly diagnosed with HCC. Furthermore, utilization of combination locoregional therapies and other more effective combination treatments, including more advanced targeted therapies, may also provide clinical benefits for patients that may translate to a cost-effective improvement in quality of life for patients with HCC. Further research regarding such cost–effectiveness of new treatment strategies is warranted.

There is little data, especially recent data, of the actual real-world costs of patients with newly diagnosed HCC and treated with LRTs in the USA in the published literature. One study of Medicare patients diagnosed with HCC during years 2000 to 2007 (34% had stage 1; 16% stage 2; 19% stage 3; 6% stage 4; 26% unstaged) who all received TACE, reported cumulative healthcare costs ranging between $74,788 and 148,878 (2011 USD), which were dependent on the number of procedures received [15]. In the study of White *et al.*, also of Medicare enrollees, in which healthcare costs were reported PPPM by HCC disease stage, those with localized disease had lower average costs PPPM ($7265; 2009 USD) compared with patients diagnosed with more advanced stages of HCC; however, they accumulated more costs over time, which was potentially attributed to longer survival durations [14]. For comparison purposes with the current study, one recently published administrative healthcare claims study examined the monthly healthcare costs of patients diagnosed with advanced HCC who were primarily treated with the systemic therapy, sorafenib; a mean cost among those who received first-line therapy of $18,381 PPPM (2015 USD) was reported [10]. This study also reported a very poor survival rate among those treated with first-line sorafenib (mean age: 62 years; 1-year survival rate: 28.5%) [10].

Additionally, there are few general estimates of the healthcare costs attributed to HCC in the USA. In 2011, the cost of an HCC-related hospitalization was estimated to be an average of $59,465, based on findings of a study using the Nationwide Inpatient Sample [20]. In an older study, using the Surveillance, Epidemiology, and End Results-Medicare linked database in 2009, reported aggregate healthcare and lost productivity costs attributed to HCC in USA were $454.9 million annually, with nearly one-half of these total illness costs attributed to patients with locoregional disease [21].

Limitations

The findings of this study must be interpreted in the context of limitations, including that the MarketScan databases consist of claims submitted by healthcare providers to insurance companies for reimbursement and are subject to coding errors either by healthcare providers or due to limitations of the database. Also, the claims data in the MarketScan databases do not contain information on tumor burden, staging of HCC, details of specific LRT procedures and their selection process, in addition to tumor response, all of which may impact the number of LRT procedures underwent and their cost. Additionally, the data source may not be representative of the US

population as a whole, with greater representation of patients residing in the South census region. The types of LRTs received and healthcare economic burden observed in this study of patients with commercial and Medicare Supplemental health plans may not generalize to other populations covered by other payer types, such as standard Medicare or Medicaid, nor may the findings of this study be applicable to those patients without insurance or who lose insurance after an HCC diagnosis. As this study was a retrospective observational analysis using claims databases, a causal relationship between the types of LRTs received and cost outcomes could not be established.

Conclusion

According to the findings of this large-scale real-world analysis of patients with newly diagnosed HCC and treated with LRT in the USA, a vast majority received at least one embolization procedure. The monthly healthcare economic burden of this patient population was relatively high ($20,316 PPPM), with 71% of healthcare costs related to HCC. The substantial monthly costs for inpatient and outpatient medical services of patients with newly diagnosed HCC and treated with locoregional therapies underscore the sizeable healthcare economic burden for payers and patients of this population. The findings of this study may be helpful in the decision-making process of defining the best therapies for patients with newly diagnosed HCC in the currently changing landscape of treatment options in the USA.

Summary points

- There is limited information available regarding the real-world treatment patterns and economic burden specifically of patients with newly diagnosed hepatocellular carcinoma (HCC) and treated with locoregional therapy (LRT), especially in the USA.
- To gain a better understanding, we conducted a retrospective observational analysis using administrative healthcare claims data to examine the real-world LRTs received, LRT treatment characteristics and the healthcare economic burden of patients with newly diagnosed HCC in the USA.
- Among 2101 patients with newly diagnosed HCC treated with LRT, a majority (77.3%) of patients received embolization therapy at any time of the follow-up periods, with 68.7% having received transarterial embolization/transarterial chemoembolization and 20.7% transarterial radioembolization; 27.3% received ablative therapy and 28.1% received radiation therapy; 30.9% of patients received multiple LRTs.
- After patients received their first LRT treatment, total all-cause healthcare costs averaged $20,316 per patient per month; 70.7% ($14,359) were HCC related.
- The substantial monthly healthcare costs of patients with newly diagnosed HCC and treated with LRTs underscore the sizeable healthcare economic burden for payers and patients of this population.
- The findings of this study may be helpful in the decision-making process of defining the best therapies in the currently changing landscape of treatment options for HCC in the USA.

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Disclaimer

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Ethical conduct of research

In compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), the databases utilized for this study consist of fully de-identified data sets, and therefore the study was exempt from institutional review board overview.

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