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ORIGINAL RESEARCH—CLINICAL

COVID-19 Pandemic Impact on Diagnosis, Stage, and Treatment of Hepatocellular Carcinoma in the United States

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BACKGROUND AND AIMS: The change in hepatocellular carcinoma (HCC) care continuum during the coronavirus disease 2019 (COVID-19) pandemic remains unknown at a national level in the United States. We sought to determine the impact of the pandemic on incident HCC cases, clinical characteristics, and treatment in the United States. **METHODS:** Using the National Cancer Database, we analyzed incident HCC cases from 2010 to 2020. The incidence rate was calculated using the population data for each year from the census bureau. Joinpoint regression analysis was applied for trend analysis, and a polynomial regression model estimated the number of projected HCC cases in 2020 according to the trend of rates from 2010 to 2019. The distribution of cancer stage and treatment modality were assessed. **RESULTS:** The pandemic led to a significant reduction in reported HCC cases, from 19,597 in 2019 to 16,188 in 2020. The projected number of HCC for 2020 was 19,011, corresponding to a 14.8% reduction in 2020. Extent of reduction in the number of incident HCC cases relative to estimated cases remains consistent in racial and ethnic subgroups. Despite underdiagnosis of HCC in 2020, proportion of patients with early tumor stage (30.5% for Tumour, Node, Metastasis stage 1) and curative treatment receipt (9.1% for surgical resection, 13% for ablation, 4.2% for liver transplant) for HCC remained stable in the first year of the COVID-19 pandemic. **CONCLUSION:** There was a significant reduction in HCC cases in 2020 compared to pre-COVID years. While tumor stage and proportion of patients receiving curative treatment remained stable, continued follow-up is needed to assess potential changes during subsequent years.

Keywords: Coronavirus Disease 2019 (COVID-19); Liver Cancer; Underdiagnosis; United States

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has had a considerable impact on healthcare systems.[1] Since the appearance of the first case in Wuhan, China, in December 2019, millions of people around the world have been infected by COVID-19.[2] Healthcare institutions have shifted their focus toward confronting the major challenges imposed by the pandemic, thus altering routine healthcare pathways.[3,4] Patients with hepatocellular carcinoma (HCC) are considered a particularly vulnerable population given their higher mortality risk.[5]

Although HCC has a high mortality, early cancer detection is associated with significantly improved curative treatment receipt and overall survival.[6–9] Patients enrolled in the HCC surveillance program are typically asymptomatic and have an increased likelihood of having early-stage HCC.[10] Thus, society guidelines including the American Association for the Study of Liver Diseases recommend semi-annual HCC surveillance.[11]

Several studies have shown a substantial alteration in HCC screening and management since the emergence of the COVID-19 pandemic.[12–15] An international observational study reported that 87% of centers modified clinical practice for liver cancer: 40.8% diagnostic procedures, 80.9% screening programs, 50% canceled curative and/or palliative treatments, and 41.7% modified liver transplantation protocols.[12] COVID-19 restrictions resulted in delays in clinic visits, diagnostic delays, fewer patients being presented to multidisciplinary tumor boards, and treatment delays.

Abbreviations used in this paper: **BCLC, Barcelona Clinic Liver Cancer; COVID-19, coronavirus disease 2019; HCC, hepatocellular carcinoma; NCDB, National Cancer Database.**

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However, little is known about how these process failures translate into changes in HCC diagnoses, early tumor detection, and curative treatment receipt at a national level in the United States. Our study aimed to describe trends in the number of incident HCC cases, tumor staging, and treatments in the United States during the early COVID-19 pandemic.

Methods

Using data from the US National Cancer Database (NCDB), we analyzed incident HCC cases in the United States from 2010 to 2020. Data on patient demographics, socioeconomic status, medical comorbidities, tumor size, stage, treatment type, treatment facility, and region were extracted.

Database

The NCDB is among the largest cancer registries in the world and is jointly sponsored by the Commission on Cancer of the American College of Surgeons and the American Cancer Society starting in 1988. It encompasses national clinical oncology data from more than 1500 facilities approved by the Commission on Cancer. Moreover, NCDB captures more than 70% of all incident cancer in the United States and implements accurate data monitoring to safeguard data quality.[16]

Inclusion Criteria and Study Period

All patients diagnosed with HCC between January 1, 2010, and December 31, 2020, were identified from the NCDB. Inclusion criteria comprised all adult patients (>18 years old) diagnosed with HCC based on the International Classification of Diseases–Oncology 3rd Edition code C22.0 and the histology codes 8170–8175.

Patients and Variables

From the NCDB, we reviewed HCC-specific variables including tumor size, stage, grade, and treatment type. Curative treatment was defined as the receipt of local ablation, surgical resection, or liver transplantation. Additionally, we retrieved covariates on patient characteristics including patient age, sex, race and ethnicity, medical comorbidities, education level, income, treatment facility type, and location. Race and ethnic groups were categorized as White, Hispanic, Black, Asian, and others. Medical comorbidities were graded by the Charlson/Deyo comorbidity index. Education level was reported as a percentage of patients without a high school diploma. Treatment facility type was classified into academic (>500 new cancer diagnoses annually and at least 4 postgraduate training programs) or nonacademic (including comprehensive community, integrated networks, and community programs). Treating facilities were classified by geographic regions within the United States (Northeast, Midwest, South, and West).

Statistical Analysis

Baseline demographic and clinical characteristics were summarized as median with interquartile range for continuous variables and as n (%) for categorical data. We obtained P values using the Kruskal-Wallis rank sum test for continuous variables and Pearson's chi-squared test for categorical variables.

The number of incident HCC cases was reported, and the incidence rate was calculated using the total population for each year from the US Census Bureau (https://data.census.gov/). Projection of the incidence rate of HCC in 2020 was performed according to the trend of rates from 2010 to 2019. We tested models including autoregressive moving average model, autoregressive integrated moving average, polynomial and linear regression. Finally, polynomial regression was selected to determine the projected incidence rates as it demonstrated the best model fit. Subsequently, we converted the incidence rate to the number of HCC patients based on the population in 2020. If the actual incidence rate was not within the 95% confidence interval (CI) of the projected incidence rate, we regarded this as a significant difference. We then calculated the percentage difference between the projected and actual incidence rate by using the following formula: (projected – actual)/projected incidence rate*100%.

To determine the projected incidence rates categorized by racial/ethnic groups, we determined the number of incident HCC cases in each subgroup, calculated the incidence rates by using the corresponding number of population for each year, and estimated the projected incidence rate using polynomial regression.

Furthermore, HCC stage and proportion of patients receiving curative treatment from 2010 to 2020 were analyzed. For HCC diagnosed between 2010 and 2017, staging was defined using the American Joint Committee on Cancer 7th edition, while the American Joint Committee on Cancer 8th edition was used for HCC diagnosed between 2018 and 2020. The proportion of patients in different HCC stages and the aggregate proportion of patients receiving curative treatment were illustrated as a stacked bar chart over time from 2010 to 2020.

Results

Baseline Characteristics

A total of 189,244 eligible patients were included. The median age was 64 years, and 76.0% were male (Table 1). The majority of patients were White (63.0%), followed by Black (15.0%), Hispanic (13.0%), and Asian/other (8.7%). Between 2010 and 2019, the median age at diagnosis increased from 63 to 67 years ($P < .001$), had an increased proportion of males ($P < .001$), and higher comorbidities (19%–22%, $P < .001$). About half of HCC patients were diagnosed at academic facilities although this decreased over time (53%–48%, $P < .001$).

Underdiagnosis of HCC in 2020

The number of HCC cases and incidence rates was significantly reduced in 2020 compared to prior years (Figure 1). Before the COVID-19 pandemic, the incidence rate of HCC cases increased from 4.22 (per 100,000 person-years) in 2010 to 6.04 in 2017, followed by a stabilized trend (6.01 in 2018 and 5.97 in 2019) then decreased to 4.91 in 2020. Projecting this trend, the predicted incidence rate of HCC in 2020 was 5.77 (95% CI: 5.64–5.90). The actual incidence rate represented a 14.8% reduction compared to the projection, and it was out of the 95% CI of the projected incidence rate. Similarly, each race and ethnic subgroup demonstrated a decreased observed HCC

Table 1. Baseline Characteristics of Patients Diagnosed With HCC

Characteristic	Overall, N = 189,244[a]	2010–2018, N = 153,459[a]	2019, N = 19,597[a]	2020, N = 16,188[a]	*P* value[b]
Age	64 (58, 72)	63 (58, 71)	66 (60, 73)	67 (61, 73)	<.001
Sex					<.001
Male	144,193 (76%)	117,140 (76%)	14,713 (75%)	12,340 (76%)	
Female	45,051 (24%)	36,319 (24%)	4884 (25%)	3848 (24%)	
Race and ethnicity					<.001
Hispanic	24,359 (13%)	19,482 (13%)	2658 (14%)	2219 (14%)	
White	116,043 (63%)	93,783 (63%)	12,132 (63%)	10,128 (64%)	
Black	28,134 (15%)	23,154 (15%)	2768 (14%)	2212 (14%)	
Asian + others	16,129 (8.7%)	13,108 (8.8%)	1679 (8.7%)	1342 (8.4%)	
Tumor size (mm)	42 (25, 73)	42 (25, 73)	42 (25, 75)	43 (26, 77)	<.001
AJCC clinical T					<.001
T1	66,841 (41%)	54,875 (42%)	6657 (39%)	5309 (38%)	
T2	40,343 (25%)	32,562 (25%)	4368 (26%)	3413 (24%)	
T3	42,887 (27%)	36,870 (28%)	3220 (19%)	2797 (20%)	
T4	11,373 (7.0%)	6002 (4.6%)	2804 (16%)	2567 (18%)	
AJCC clinical N					.005
N0	150,838 (91%)	122,128 (91%)	15,856 (91%)	12,854 (90%)	
N1	14,814 (8.9%)	11,884 (8.9%)	1551 (8.9%)	1379 (9.7%)	
AJCC clinical M					<.001
M0	151,233 (86%)	122,306 (86%)	15,951 (86%)	12,976 (85%)	
M1	24,245 (14%)	19,343 (14%)	2631 (14%)	2271 (15%)	
Treatment					<.001
Ablation	21,075 (11%)	16,526 (11%)	2495 (13%)	2054 (13%)	
Resection	16,688 (8.9%)	13,457 (8.8%)	1775 (9.1%)	1456 (9.1%)	
Transplant	10,664 (5.7%)	9126 (6.0%)	861 (4.4%)	677 (4.2%)	
Other noncurative treatment/best supportive care	139,563 (74%)	113,346 (74%)	14,329 (74%)	11,888 (74%)	
Comorbidity					<.001
0	88,192 (47%)	71,799 (47%)	9046 (46%)	7347 (45%)	
1	43,095 (23%)	35,667 (23%)	4021 (21%)	3407 (21%)	
2	20,303 (11%)	16,124 (11%)	2309 (12%)	1870 (12%)	
3	37,654 (20%)	29,869 (19%)	4221 (22%)	3564 (22%)	
Grade					<.001
1	20,227 (32%)	16,955 (32%)	1826 (34%)	1446 (31%)	
2	29,081 (47%)	24,302 (46%)	2481 (46%)	2298 (49%)	
3	12,580 (20%)	10,604 (20%)	1030 (19%)	946 (20%)	
4	629 (1.0%)	587 (1.1%)	31 (0.6%)	11 (0.2%)	
Education (% nO HSD)					.003
15.3% +	50,337 (31%)	41,151 (31%)	5064 (31%)	4122 (30%)	
9.1%–15.2%	47,874 (30%)	38,877 (29%)	4860 (29%)	4137 (31%)	
5.0%–9.0%	39,812 (25%)	32,254 (24%)	4176 (25%)	3382 (25%)	
<5.0%	23,909 (15%)	19,617 (15%)	2386 (14%)	1906 (14%)	
Income					.154
<$46,277	37,443 (23%)	30,538 (23%)	3781 (23%)	3124 (23%)	
$46,277–$57,856	36,907 (23%)	29,920 (23%)	3828 (23%)	3159 (23%)	
$57,857–$74,062	37,903 (23%)	30,805 (23%)	3873 (24%)	3225 (24%)	
$74,063 +	49,202 (30%)	40,241 (31%)	4957 (30%)	4004 (30%)	
Facility type					<.001
Non academic	89,459 (47%)	71,409 (47%)	9686 (49%)	8364 (52%)	
Academic	99,785 (53%)	82,050 (53%)	9911 (51%)	7824 (48%)	
Location					<.001
Northeast	37,674 (20%)	31,024 (20%)	3621 (19%)	3029 (19%)	
Midwest	37,612 (20%)	30,325 (20%)	3989 (21%)	3298 (21%)	
South	74,932 (40%)	60,189 (40%)	8034 (42%)	6709 (42%)	
West	36,734 (20%)	30,119 (20%)	3685 (19%)	2930 (18%)	

Overall missing data from baseline categories including race/ethnicity (n = 4579), tumor size (n = 34,084), AJCC clinical T (n = 27,800), AJCC clinical N (n = 23,592), AJCC clinical M (n = 13,766), treatment (n = 1254), grade (n = 126,727), education (n = 27,312), income (n = 27,789), and location (n = 2292).

AJCC, American Joint Committee on Cancer; HSD, high school degree.

[a]Median (IQR); n (%).

[b]Kruskal-Wallis rank sum test; Pearson's chi-squared test.

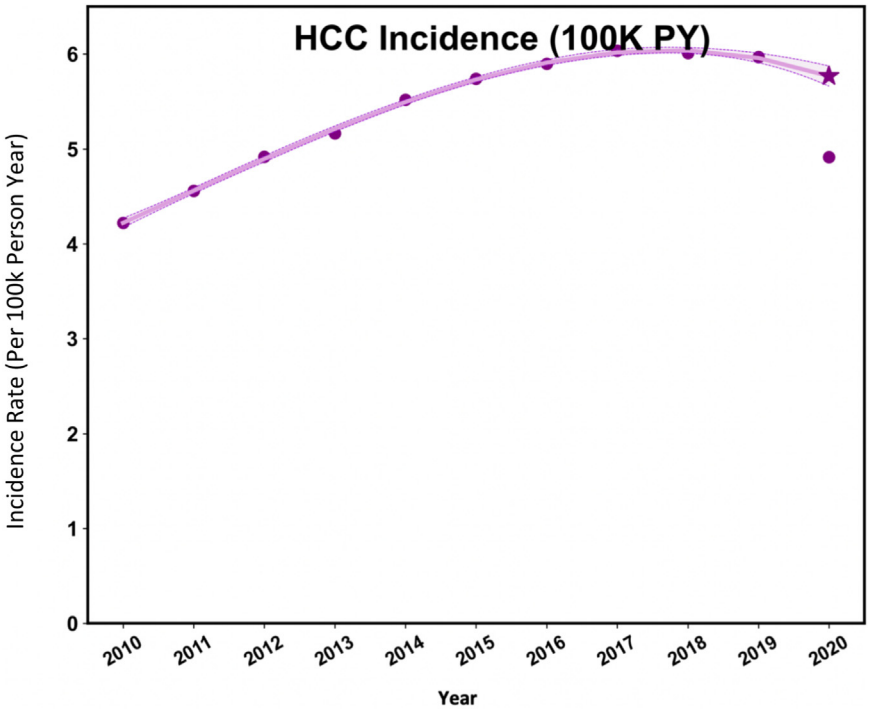

Figure 1. Hepatocellular carcinoma incidence per 100,000 person year. The dots denote the actual incidence rates from 2010 to 2020. The star denotes the predicted incidence rate in 2020.

incidence in 2020. The percent reduction for White, Hispanic, Black, and Asian/other subgroups were 13.2%, 11.8%, 11.6%, and 11.4%, respectively, highlighting that there was no significant racial/ethnic disparity in the magnitude of HCC underdiagnosis in 2020.

Tumor Stage Distribution and Curative Treatment Receipt

The distribution of HCC stage over time from 2010 to 2020 is illustrated in (Figure 2). There were no significant changes in tumor stage, with stable proportions of early-stage HCC. Prior to the COVID-19 pandemic (2010–2018), the median proportion of HCC stage 1, 2, 3, and 4 was 33.1%, 18.4%, 18.8%, and 16.6%, respectively. In 2020, Tumour, Node, Metastasis stage remained stable at 30.5%, 18.5%, 21.0%, and 18.4%, respectively. The median tumor size in 2020 was 4.3 cm (interquartile range = 2.6 cm–7.7 cm), which has been stable during the study period (Figure 3).

The proportion of curative treatment also appeared stable over time (Figure 4). The proportion of patients receiving liver transplantation slightly decreased from 6.0% to 4.2% ($P < .001$), although the proportions undergoing ablation and resection increased (ablation 11%–13%; resection 8.8%–9.1%, $P < .001$ for both).

Discussion

In this large nationwide study using NCDB, we showed a 14.8% reduction in the incidence of HCC in 2020 relative to the predicted incidence of HCC. However, overall proportions of tumor stage and curative treatment remained stable in 2020.

The COVID-19 pandemic produced an altered allocation of healthcare resources which may be the cause of several problems within the healthcare system, including cancer screening interruption, treatment cancellations, follow-up delays, and patient fears. One study of US Medicare cancer patients found that during the post-COVID-19 period, there was a significant decrease in screening including breast, colon, lung, and prostate cancers.[17] In terms of liver cancer, a survey-based cohort study assessed the impact of COVID-19 in 14 Asia-Pacific countries and observed a 26.7% decline in new HCC cases during the pandemic compared to the prepandemic.[13] A large study of the Veterans Health Administration in the United States reported that HCC screening and diagnosis rates declined by 44% and 13%, respectively, after the COVID-19 pandemic.[18] Similarly, our study showed a 14.8% reduction in the incidence of HCC when compared to the estimated incidence of HCC (Figure 1). There were no significant racial-ethnic disparities in HCC underdiagnosis in 2020 vs pre-COVID years.

We calculated this incidence rate using the total population for each year from the US Census Bureau taking into account population changes related to special circumstances (ie natural disasters like the COVID-19 pandemic). One study reported almost 700,000 excess deaths in the United States from March 1, 2020, through February 28, 2021.[19] In addition to the substantial excess death, the disproportionally high toll of deaths in patients with chronic liver disease and cirrhosis during this period could further contribute to the decrease in incident HCC.[20] As individuals with chronic liver and cirrhosis account for the majority of the incident HCC, excess mortality in this subpopulation could result in being partly responsible for the decreased rate of detection of HCC during our study time period.

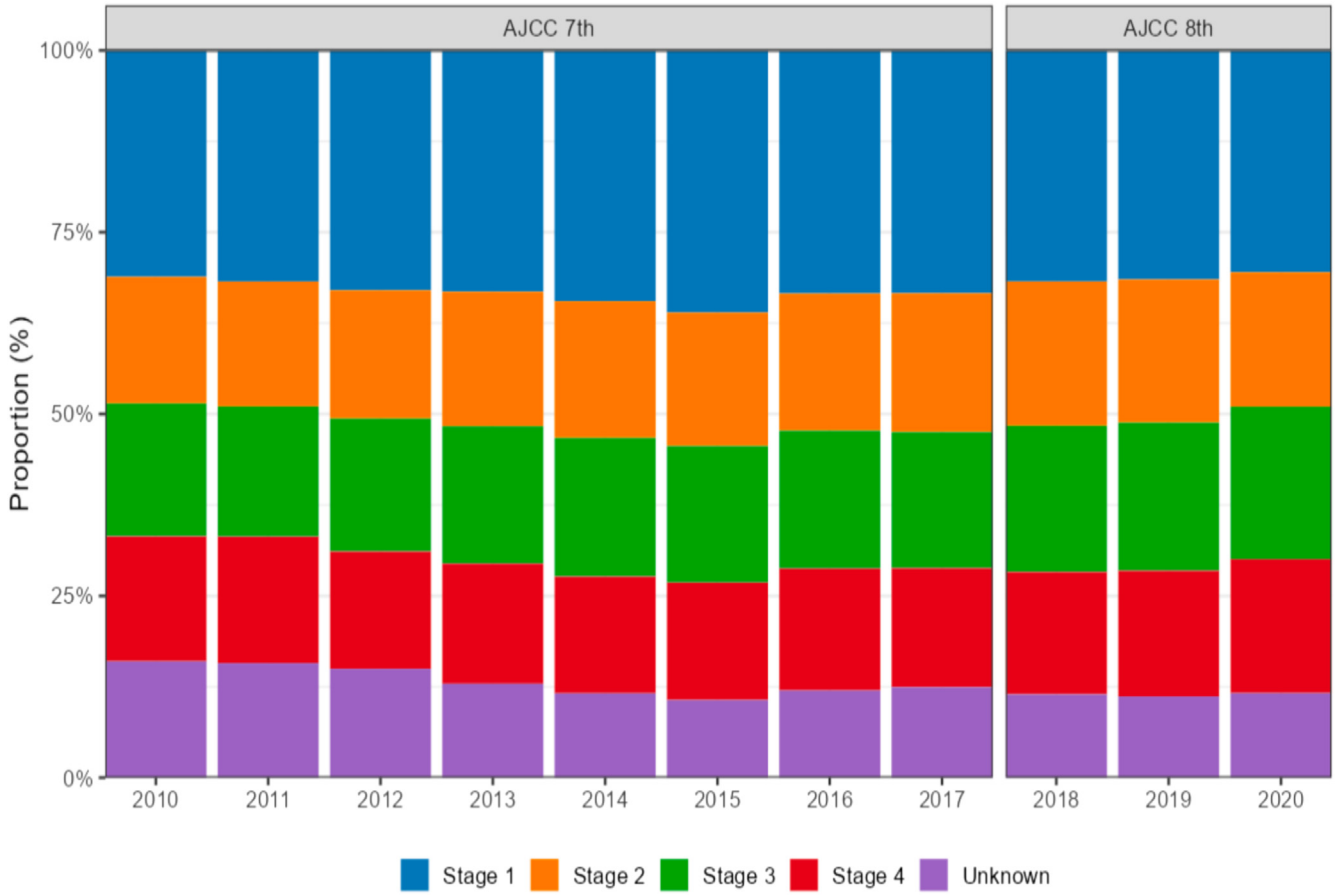

Figure 2. The proportion of patients in different hepatocellular carcinoma (HCC) stages. For HCC diagnosed between 2010 and 2017, the staging was defined using AJCC 7th edition, while AJCC 8th edition was used for HCC diagnosed between 2018 and 2020. AJCC, American Joint Committee on Cancer.

Lum *et al* reported a significant reduction in all incident cancers, especially early-stage cancers, between March and May 2020. This paper showed a systematic decrease in cancer incidence that is thought to be multifactorial and related to the relative role of cancer prevention, screening, early detection, and resource constraints amid the COVID-19 pandemic.[21]

Despite the implementation of COVID-19-associated healthcare restrictions, tumor stage and proportion of patients receiving curative treatment remained largely stable during the first year of the COVID-19 pandemic. Prior studies had predicted that the effects of COVID-19 on healthcare access would result in migration to higher stages of disease and an overall increase in cancer mortality.[17] One small study reported fewer Barcelona Clinic Liver Cancer (BCLC) stage 0-B HCCs in the pandemic year.[22] However, another study reported an increase in BCLC A and B and a decrease in detection of BCLC C and D HCC during the COVID-19 pandemic, however, this was statistically insignificant ($P = .143$).[23] Similar to our study, Ribaldone *et al* reported a sharp decline in new HCC diagnoses in the first 2 years of the pandemic, however, there was no observed change in tumor stage.[24] Interestingly, in a multicenter retrospective study by Amaddeo *et al*, there was a shorter interval between the multidisciplinary tumor board discussion and treatment in 2020 vs 2019.[15] Another study reported lower surgical resectability rates in patients with liver cancer during the initial phase of the COVID-19 pandemic that promptly recovered to pre-COVID-19 levels after 6 months.[23] A small study in Northern England showed that although HCC incidence was reduced, patients continued to receive treatment appropriate to cancer stage with shorter waiting times.[22] These studies may suggest that physicians tend to treat patients with HCC more quickly despite the COVID-19 pandemic. Additionally, many guidelines, including the American Association for the Study of Liver Diseases Expert Panel Consensus Statement, encouraged providers to consider virtual patient visits to discuss the diagnosis and management of HCC, as well as, proceeding with HCC treatment.[25] For early-stage HCC, patients may benefit from curative treatment (resection, ablation, transplant) which may offer 5-year survival exceeding 70%.[26,27] In patients with HCC, the treatment is determined according to tumor stage, therefore both the proportion of early tumor stage and curative treatment were similarly unchanged by the COVID-19 pandemic according to our study.[27] Although our study did not show a stage migration to advanced diseases, this should be further evaluated in future studies. Considering that HCC is a relatively

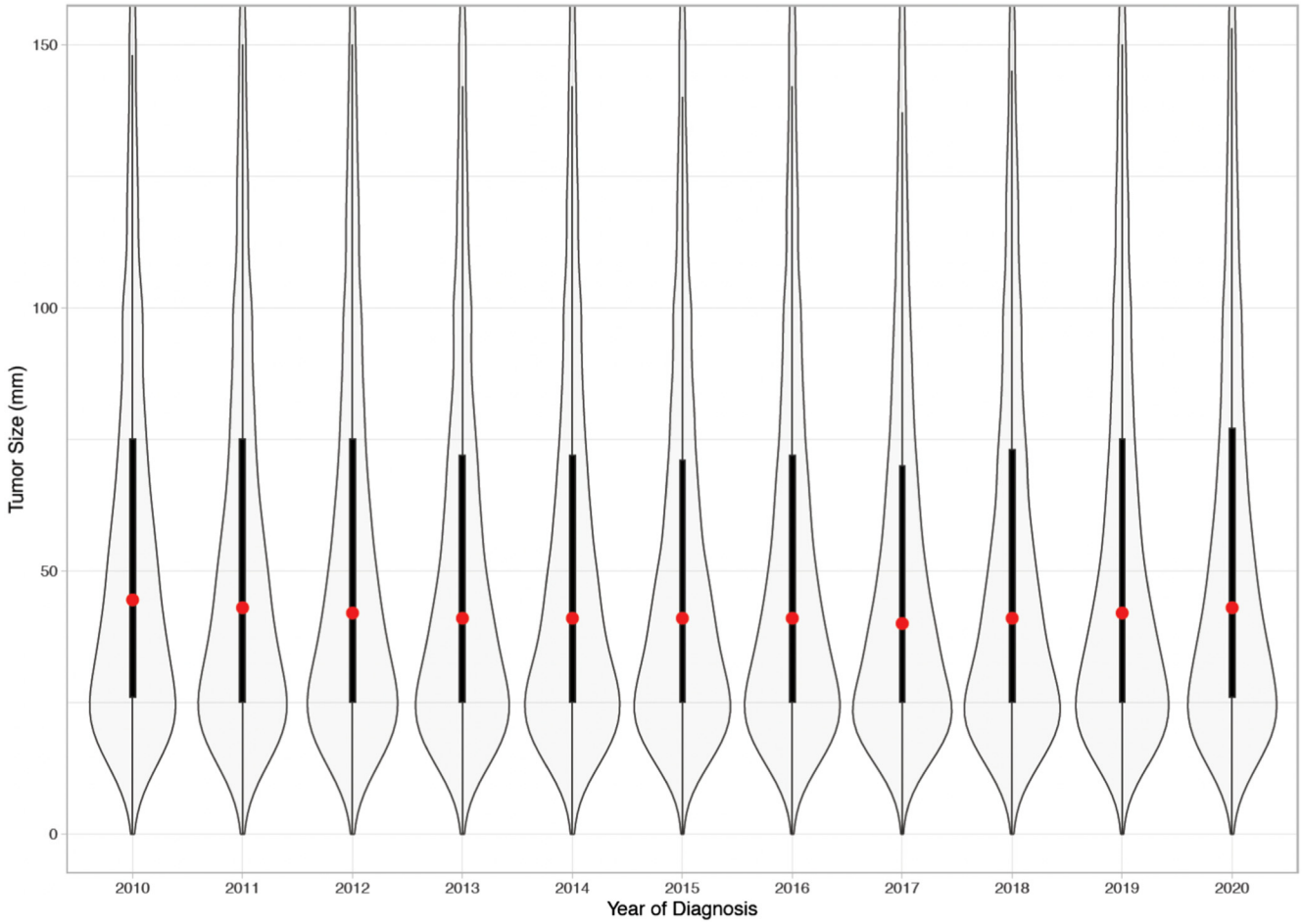

Figure 3. Median tumor size in patients with hepatocellular carcinoma (HCC). Bell shape represents inverted histogram (majority of the tumor size falls around the widest region). Red dot denotes median number. Upper portion of the black line represents the 75th quartile and lower portion represents the 25th quartile.

slow-growing cancer with a tumor volume doubling time of approximately 4–6 months, the clinical consequences of missed diagnosis may be more evident in future studies.[24,28]

The COVID-19 pandemic significantly impacted the care of patients with HCC in healthcare institutions across the world; however, the extent of the impact varies based on country-specific measures instituted to manage the pandemic. This study is the first of its kind to measure the extent of the impact of COVID-19 on the diagnosis and treatment of HCC patients in the United States using a large NCDB. Overall, a statistically significant reduction in reported cases of HCC in 2020 vs pre-COVID years was seen although no significant changes in tumor stage or curative treatment were noted. A potential factor contributing to the decreased overall incidence of HCC during this period is the disparities in access to medical imaging and variations in radiology techniques influenced by pre-existing socioeconomic factors. One retrospective study reported that, when compared to 2019, the total imaging volume in the post-COVID-19 period of 2020 exhibited statistically significant changes in imaging utilization patterns. Notably, patients aged 60–79, males, non-White individuals, those covered by Medicaid or uninsured, and those with incomes below $80,000 demonstrated increased imaging utilization. Conversely, there was a notable decrease in imaging utilization among younger patients (<18 years old), females, White individuals, those with commercial insurance, and those with incomes ≥$80,000.[29] Moreover, the identification of socioeconomic health disparities linked to imaging utilization may represent an initial step in recognizing the need for imaging resources among specific patient groups during a healthcare crisis and its subsequent recovery. The reduction in HCC cases may also be in part due to a lack of proper semiannual screenings as noted in prior studies.[12,14] A large international survey from March 2020 to June 2020 reported that screening programs were modified or canceled in 80.9% of participating international centers.[12] Furthermore, a study on the NCDB reported a significant reduction in all incident cancer in the months of 2020 followed by an increase in late-stage cancer in the later months of 2020.[21] Thus, further data on HCC cases from subsequent years (ie 2021–2023) are needed to determine whether there was a decreased detection with a delayed spike in rates in the following years.

The strengths of our study include a large sample size as it is a nationwide study with racially, ethically, and

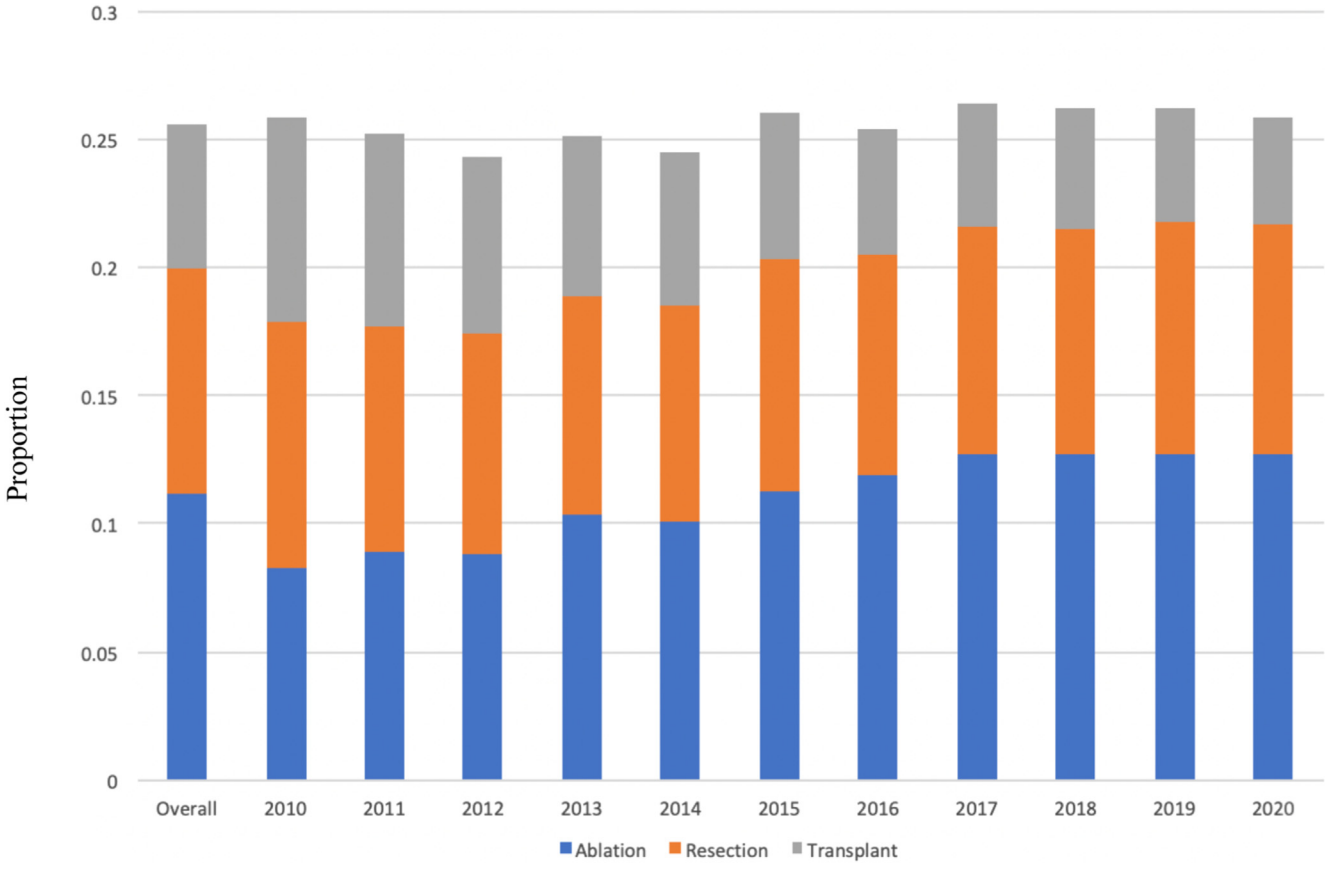

Figure 4. Curative treatment proportion in patients with hepatocellular carcinoma (HCC).

socioeconomically diverse population. Moreover, the NCDB has been a reliable source for reported cancer cases even during the COVID-19 pandemic (2020).[30]

We recognize the limitations of this study. Our cohort reflects the early COVID pandemic, and we did not have data for patients diagnosed with HCC in the later years of the pandemic. There may be limitations with the HCC data registry associated with COVID-19 restrictions, including delays in data entry, nursing follow-up, inter-institution communication, and registras''ability to report data. However, Nogueira et al reviewed the impact of the COVID-19 pandemic on the reliability of the NCDB and noted that the significant deficit in the number of cancer diagnoses in 2020 was not due to cancer registrars' inability to extract data during the pandemic. Further studies are needed to determine the impact of the pandemic on the reliability of data collected by other national cancer registries.[30] Other limitations include a lack of survival information, so we were unable to assess the prognostic impact of the COVID-19 pandemic in HCC patients. Additionally, we only included HCC patients in the United States, so our study findings might not be generalized to patients outside of the United States.

Conclusion

In conclusion, there was a significant reduction in incident HCC cases in 2020 vs prepandemic years in the United States. Tumor stage and proportion of patients receiving curative treatment remained stable in 2020 despite limitations imposed by COVID-19, although continued follow-up is needed to see if these findings remain stable in later years of the pandemic.

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Ju Dong Yang: Study design and study supervision. Bhupinder Kaur, Yee Hui Yeo, Michael Luu: Data analysis. Bhupinder Kaur, Yee Hui Yeo, Jeff Liang, Michael Luu, Ju Dong Yang: Drafting of the manuscript. All authors contributed to data interpretation, critical revisions, and approval of the final manuscript.

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These authors disclose the following: Jun Gong: Consultant or Advisory Role – EMD Serono, Elsevier, Exelixis, QED Therapeutics, Natera, Basilea, HalioDx, Eisai, Janssen, Aveo, Seagen, Pfizer, and Bayer, all outside of the submitted work. Ju Dong Yang: Consultant or Advisory Role –AstraZeneca, Eisai, Exact Sciences, Exelixis, Fujifilm Medical Sciences, Merck and Gilead Sciences ai, Eximus, Fujifilm, and Gilead Sciences, all outside of the submitted work. Amit Singal has served as a consultant or on advisory boards for Genentech, AztraZeneca, Eisai, Bayer, Exelixis, Boston Scientific, FujiFilm Medical Sciences, Exact Sciences, Roche, Glycotest, Freenome, and GRAIL. The remaining authors disclose no conflicts.

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Ethical approval and consent were not required as this study was based on publicly available data.

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Data, analytic methods, and study materials will not be made available to other researchers as data is owned by NCDB and requires special permission to get access.

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