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Authors
Lee, Yi-Te
Wang, Jasmine J
Luu, Michael
et al.

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The Mortality and Overall Survival Trends of Primary Liver Cancer in the United States

Yi-Te Lee (ID), MD,[1,2] Jasmine J. Wang (ID), MD,[2,3] Michael Luu (ID), MPH,[4] Mazen Noureddin, MD,[5,6] Kambiz Kosari (ID), MD,[6] Vatche G. Agopian, MD,[7,8] Nicole E. Rich (ID), MD, MS,[9] Shelly C. Lu, MD,[3,5] Hsian-Rong Tseng (ID), PhD,[1,2] Nicholas N. Nissen, MD,[3,6] Amit G. Singal, MD, MS,[9] Ju Dong Yang, MD, MS,[3,5,6,*]

[1]California NanoSystems Institute, Crump Institute for Molecular Imaging, University of California, Los Angeles, Los Angeles, CA, USA; [2]Department of Molecular and Medical Pharmacology, University of California, Los Angeles, Los Angeles, CA, USA; [3]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [4]Biostatistics and Bioinformatics Research Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [5]Karsh Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [6]Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [7]Department of Surgery, University of California, Los Angeles, Los Angeles, CA, USA; [8]Jonsson Comprehensive Cancer Center, University of California, Los Angeles, Los Angeles, CA, USA and [9]Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, TX, USA

*Correspondence to: Ju Dong Yang, MD, MS, Karsh Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, 8900 Beverly Blvd, Los Angeles, CA 90048, USA (e-mail: judong.yang@cshs.org).

Abstract

Background: Recent trends of hepatocellular carcinoma (HCC) mortality and outcome remain unknown in the United States. We investigated the recent trends of primary liver cancer (excluding intrahepatic cholangiocarcinoma) mortality and HCC stage, treatment, and overall survival (OS) in the United States. **Methods:** The National Center for Health Statistics Database was analyzed to investigate the trend of primary liver cancer mortality. We analyzed the Surveillance, Epidemiology, and End Results 18 Database to assess the temporal trend of tumor size, stage, treatment, and OS of HCC. We investigated the association between HCC diagnosis year and OS using Cox regression analysis. All statistical tests were 2-sided. **Results:** During 2000-2018, liver cancer mortality rates increased until 2013, plateaued during 2013-2016 (annual percent change = 0.1%/y, 95% confidence interval [CI] = −2.1%/y to 2.4%/y, P = .92), and started to decline during 2016-2018 (annual percent change = −1.5%/y, 95% CI = −3.2%/y to 0.2%/y, P = .08). However, mortality continues to increase in American Indian and Alaska Native, individuals aged 65 years or older, and in 33 states. There was a 0.61% (95% CI = 0.53% to 0.69%, P < .001) increase in localized stage HCC and a 0.86-mm (95% CI = −1.10 to −0.62 mm, P < .001) decrease in median tumor size per year. The 1-year OS rate increased from 36.3% (95% CI = 34.3% to 38.3%) to 58.1% (95% CI = 56.9% to 59.4%) during 2000-2015, and the 5-year OS rate almost doubled from 11.7% (95% CI = 10.4% to 13.1%) to 21.3% (95% CI = 20.2% to 22.4%) during 2000-2011. Diagnosis year (per year) (adjusted hazard ratio = 0.96, 95% CI = 0.96 to 0.97) was independently associated with OS in multivariable analysis. **Conclusions:** Primary liver cancer mortality rates have started to decline in the United States with demographic and state-level variation. With an increasing detection of localized HCC, the OS of HCC has improved over the past decades.

Primary liver cancer remains the fourth-leading cause of cancer-related death worldwide (1,2). Most primary liver cancers (>80%) are hepatocellular carcinoma (HCC), with intrahepatic cholangiocarcinoma (iCCA) being the second-most common and accounting for 10%-15% (2). The majority of HCCs occur in patients with cirrhosis, which can be due to several etiologies, including chronic hepatitis B virus (HBV), hepatitis C virus (HCV), heavy alcohol use, or nonalcoholic fatty liver disease. HCC incidence rates in the United States increased over several decades; however, recent data from the Surveillance, Epidemiology, and End Results (SEER) Program showed incidence rates plateaued in 2013 and then started to decline in 2016 (3,4).

Small improvement in HCC survival during the 1970s to 2011 in the United States has been attributed to increased earlier detection, refinement of staging systems and treatment allocation algorithms, and improvement in HCC therapies (5,6). With gradual improvements in HCC surveillance, it is anticipated that

more patients will be diagnosed at early stages and therefore able to receive curative treatments (7). Although a previous modeling study in 2014 reported that liver cancer incidence and mortality would continue to increase by 2030 in the United States (8), it is possible that liver cancer mortality rates may instead plateau or decline sooner than previously anticipated due to a decrease in HCC incidence and improvement in overall survival (OS).

An earlier study indicated substantial demographic and regional variation in the burden of HCC due to the difference in the prevalence of risk factors, access to care, and socioeconomic disparities; however, there are fewer data evaluating disparities in HCC prognosis (2). The aim of this study is to investigate the recent temporal trends of demographic and state-level variation in primary liver cancer mortality (excluding iCCA), and tumor burden, receipt of curative treatment, and OS of HCC in the United States.

Methods

Data Sources

US Cancer Mortality data between 2000 and 2018, collected and maintained by the National Center for Health Statistics (NCHS) (9), were curated and analyzed using SEER*Stat software (10). Although this database included nationwide mortality data, mortality statistics specific for HCC are not available. To estimate the trend of HCC mortality, we reported primary liver cancer mortality excluding iCCA by International Classification for Diseases (ICD) version 10 codes for the underlying cause of death using codes C22.0–C22.9 (malignant neoplasm of liver and intrahepatic bile ducts), excluding C22.1 (iCCA) (11).

We assumed that the trend of primary liver cancer mortality excluding iCCA from the NCHS Database (9) would reflect the trend of national HCC mortality. Therefore, we performed a sensitivity analysis using the SEER 18 Database (12) to assess the accuracy of our estimates and calculate the HCC-specific incidence-based (IB) mortality rate during 2000-2017 by linking the characteristics of HCC at diagnosis to the death certificate (5,13). HCC cases were identified using ICD for Oncology, 3rd edition, codes (site: C22.0; histology: 8170–8175). HCC stage, tumor size, types of treatment, and survival data were also curated from SEER 18 Database (12).

Study Variables

The study variables included sex, age, race or ethnicity(non-Hispanic White, Black, American Indian and Alaska Native [AI and AN], Asian and Pacific Islander [API], and Hispanic), state, tumor stage, diameter of the largest tumor (available since 2004), the proportion receiving curative treatments, and OS. SEER Summary Stage 2000 was used for HCC staging: localized (confined to liver), regional (spread to regional lymph nodes), and distant (extrahepatic metastasis) stages (12).

Statistical Analyses

Mortality rates, tumor stage, largest tumor size, curative treatment, and OS data were ascertained using SEER*Stat software (version 8.3.6.1) (10). Mortality rates were age adjusted to the 2000 US standard population and expressed per 100 000 person-years (PY) (14,15). Primary liver cancer mortality rates were calculated as the number of deaths attributed to liver cancer

excluding iCCA over person-time at-risk individuals in the US general population using the NCHS Database (9). HCC IB mortality rate was calculated as the number of deaths attributed to HCC over person-time at-risk individuals by linking the characteristics of HCC at diagnosis to the death certificate in the SEER-18 regions (12). Attribution to HCC was made when the cause of death on the death certificate was liver cancer ICD 10 codes C22.0–C22.9 (malignant neoplasm of liver and intrahepatic bile ducts), excluding C22.1 (intrahepatic bile duct cancer), and the deceased was listed in the registry as having been diagnosed with HCC (site: C22.0; histology: 8170–8175) at an earlier time.

The National Cancer Institute's Joinpoint Regression Analysis program (version 4.8.0.1) was used to quantify trends in primary liver cancer mortality overall and by sex, age, race or ethnicity, and state (16). The best-fitting log-linear regression model was applied to calculate annual percentage changes (APCs) and 95% confidence intervals (CIs) and identify the calendar years (ie, the joinpoints) when APCs changed statistically significantly ($P < .05$). We reported average APC (AAPC), which is a summary measure of the trend over a prespecified fixed interval and was computed as a weighted average of the APCs from the joinpoint model, with the weights equal to the length of the APC interval (17).

For survival analyses, patients who had less than 1 month follow-up period after diagnosis, diagnosed on the basis of a death certificate only or newly diagnosed at autopsy, were excluded. One-, 3-, and 5-year OS were estimated separately for each HCC year of diagnosis between 2000 and 2015 according to the Kaplan-Meier method. Trends in OS were estimated using a weighted linear model with inverse-variance weighting of the standard errors obtained from the OS estimates using the Kaplan-Meier estimator (18). Cox proportional hazard models were used to investigate the association between HCC diagnosis year and OS after adjusting for sex, age, race or ethnicity, state, tumor stage, and receipt of curative treatment. Missing values for variables in the multivariable model were imputed using chained equations algorithm as proposed by Van Buuren and Groothuis-Oudshoorn (19). A total of 5 complete data sets were generated, and the regression estimates are the average coefficients among each of the complete data and variance equal to the imputation-corrected variance-covariance matrix. The proportional hazards assumption was assessed both graphically and quantitatively using the scaled Schoenfeld residuals and the goodness-of-fit test as proposed by Grambsch and Therneau (20). All survival analyses were performed using R statistical software (version 4.0.2; R Foundation, Vienna, Austria) with 2-sided tests and a statistical significance level of .05.

Results

Trends of Primary Liver Cancer Mortality in the United States

During 2000-2018, a total of 289 567 deaths were attributed to primary liver cancer, with an overall mortality rate of 4.5 per 100 000 PY (95% CI = 4.5 to 4.5). Trends in liver cancer mortality are shown in Table 1 and Figure 1. Nationally, liver cancer mortality increased with an AAPC of 1.5%/y (95% CI = 1.1%/y to 1.9%/y, $P < .001$); however, we noted variation over the study period. Specifically, mortality rates initially increased by 1.9%/y (95% CI = 1.5%/y to 2.3%/y, $P < .001$) during 2000-2007, 2.7%/y (95% CI = 2.2%/y to 3.3%/y, $P < .001$) during 2007-2013, plateaued during 2013-2016 (APC = 0.1%/y, 95% CI = −2.1%/y to 2.4%/y,

Table 1. Age-adjusted primary liver cancer mortality rates and joinpoint trends, 2000-2018, by sex, age, and race or ethnicity in the NCHS Database

Characteristic	Mortality rates per 100 000 PY			Trend 1[a]			Trend 2			Trend 3			2000-2018 AAPC	
	2000	2016	2018	Years	APC (95% CI)	P	Years	APC (95% CI)	P	Years	APC (95% CI)	P	AAPC (95% CI)	P[b]
Overall[c]	3.7	4.9	4.8	2000-2007	1.9 (1.5 to 2.3)	<.001	2007-2013	2.7 (2.2 to 3.3)	<.001	2013-2016	0.1 (−2.1 to 2.4)	.92	1.5 (1.1 to 1.9)	<.001
Sex														
Male	5.7	7.7	7.6	2000-2013	2.6 (2.3 to 2.8)	<.001	2013-2018	−0.3 (−1.1 to 0.4)	.39	—	—	—	1.8 (1.5 to 2.0)	<.001
Female[c]	2.1	2.5	2.4	2000-2005	1.2 (0.5 to 1.9)	.005	2005-2008	−0.5 (−3.6 to 2.6)	.71	2008-2014	2.6 (2.0 to 3.3)	<.001	0.9 (0.3 to 1.4)	.001
Age, y														
<50	0.6	0.3	0.3	2000-2018	−3.7 (−4.1 to −3.3)	<.001	—	—	—	—	—	—	−3.7 (−4.1 to −3.3)	<.001
50-64	6.2	11.2	9.7	2000-2012	5.6 (5.3 to 6.0)	<.001	2012-2016	−1.4 (−3.2 to 0.5)	.14	2016-2018	−7.6 (−11.2 to −3.9)	.001	2.5 (1.9 to 3.1)	<.001
≥65	18.4	23.9	24.9	2000-2007	0.8 (0.4 to 1.2)	<.001	2007-2018	2.2 (2.1 to 2.4)	<.001	—	—	—	1.7 (1.5 to 1.8)	<.001
Race or ethnicity														
Non-Hispanic White	3.0	4.1	4.1	2000-2007	1.9 (1.5 to 2.3)	<.001	2007-2014	2.7 (2.3 to 3.2)	<.001	2014-2018	−0.7 (−1.5 to 0.1)	.07	1.6 (1.4 to 1.9)	<.001
Non-Hispanic Black	5.3	7.0	6.5	2000-2013	2.4 (2.1 to 2.8)	<.001	2013-2018	−1.7 (−2.7 to −0.7)	.003	—	—	—	1.3 (0.9 to 1.6)	<.001
Non-Hispanic AI and AN	6.0	8.0	7.6	2000-2018	2.2 (1.4 to 3.0)	<.001	—	—	—	—	—	—	2.2 (1.4 to 3.0)	<.001
Non-Hispanic API	9.8	6.8	6.0	2000-2014	−1.5 (−2.0 to −0.9)	<.001	2014-2018	−5.3 (−8.4 to −2.2)	.003	—	—	—	−2.3 (−3.1 to −1.6)	<.001
Hispanic	6.3	7.5	7.5	2000-2012	1.5 (1.0 to 2.0)	<.001	2012-2018	−0.2 (−1.2 to 0.7)	.59	—	—	—	0.9 (0.5 to 1.3)	<.001

[a]Joinpoint software selected joinpoint when annual percentage changed statistically significantly (P < .05). Thus, subgroups with steady incidence trend over the study period have only 1 trend. AAPC = average annual percent change; AI and AN = American Indian and Alaska Native; APC = annual percent change; API = Asian and Pacific Islander; CI = confidence interval; HCC = hepatocellular carcinoma; NCHS = National Center for Health Statistics; PY = person-years.
[b]A 2-sided Wald's test was used to calculate the P values and test for statistically significant trends.
[c]There were more than 3 joinpoint trends. The fourth trend for overall primary liver cancer mortality was −1.5 (95% CI = −1.9 to −0.6, P = .003) during 2014-2018. The fourth trend for female primary liver cancer mortality was −1.2 (95% CI = −3.2 to 0.2, P = .08) during 2016-2018.

P = .92), and then started to decline during 2016-2018 (APC = −1.5%/y, 95% CI = −3.2%/y to 0.2%/y, P = .08). In subgroup analyses, mortality rates recently declined in women, Blacks and APIs, and individuals aged younger than 65 years; plateaued in males, Whites, and Hispanics; and increased in AIs and ANs and individuals aged 65 years and older.

There was notable state-level variation in primary liver cancer mortality (Figure 2). In 2000, mortality rates were highest in Alaska (5.7 per 100 000 PY, 95% CI = 3.4 to 9.0 per 100 000 PY) and lowest in Kansas (1.7 per 100 000 PY, 95% CI = 1.3 to 2.3 per 100 000 PY), with a mortality rate ratio of 3.4 between the 2 states. State-level variation in mortality rates decreased in 2018, with a mortality rate ratio of 2.8 between states with the highest (Mississippi at 7.5 per 100 000 PY, 95% CI = 6.6 to 8.4 per 100 000 PY) and lowest (Nebraska at 2.7 per 100 000 PY, 95% CI = 2.1 to 3.5 per 100 000 PY) mortality. Mortality continued to increase in 33 states, plateaued in 15 states and the District of Columbia, and decreased in 2 states in recent years (Supplementary Table 1, available online). Notably, 15 states with plateaued mortality had larger populations and showed downtrending mortality that did not reach statistical significance.

Sensitivity analyses using the SEER 18 Database revealed HCC IB mortality trends in the SEER regions are comparable with the primary liver cancer mortality trend of the entire United States. Similar to the national trend of liver cancer mortality, HCC IB mortality rates increased until 2013 and then plateaued during 2013 and 2017 (APC = −0.7%, 95% CI = −2.3% to 0.9%, P = .36). Subgroup analyses showed mortality rates recently declined in APIs (2012-2017; APC = −3.5%, 95% CI = −4.9% to −1.9%, P < .001) and individuals aged younger than 50 years (2003-2017; APC = −5.0%, 95% CI = −5.9% to −4.2%, P < .001) and 50-64 years (2013-2017; APC = −4.9%, 95% CI = −8.0% to −1.7%, P = .007); plateaued in males (2012-2017; APC = −0.1%, 95% CI = −1.4% to 1.2%, P = .84), Whites (2014-2017; APC = −1.8%, 95% CI = −4.4% to 1.0%, P = .18), Blacks (2013-2017; APC = −2.6%, 95% CI = −7.3% to 2.2%, P = .25), and Hispanics (2013-2017; APC = −0.9%, 95% CI = −4.2% to 2.6%, P = .58); and increased in females (2002-2017; APC = 2.8%, 95% CI = 2.3% to 3.3%, P < .001), AIs and ANs (2000-2017; APC = 5.4%, 95% CI = 3.9% to 6.8%, P < .001), and individuals aged older than 65 years (2002-2017; APC = 3.8%, 95% CI = 3.4% to 4.1%, P < .001).

Trends of HCC Tumor Burden and Curative Treatment in the United States

Over the entire study period, more than one-half (56.8%, 95% CI = 56.5% to 57.2%) of tumors were detected at a localized stage, and approximately one-fourth (27.0%, 95% CI = 26.7% to 27.3%) of patients received potentially curative treatment (Table 2). A higher proportion of male and Black individuals presented with more advanced stage HCC and were less likely to receive curative treatment. There was also state-level variation in tumor stage and receipt of curative treatment, with the highest proportion of curative treatment receipt among patients in Alaska (40.0%, 95% CI = 30.6% to 50.0%) and lowest in New Mexico (20.1%, 95% CI = 18.3% to 21.9%).

An increasing proportion of tumors was detected at a localized stage over time (Figure 3, A). There was an annual 0.61% (95% CI = 0.53% to 0.69%, P < .001) increase in localized stage detection, increasing from 49.4% (95% CI = 47.2% to 51.7%) in 2000 to 60.8% (95% CI = 59.4% to 62.1%) in 2016. This trend was seen in all demographic subgroups except AIs and ANs (Supplementary Table 2, available online). Similarly, there was a
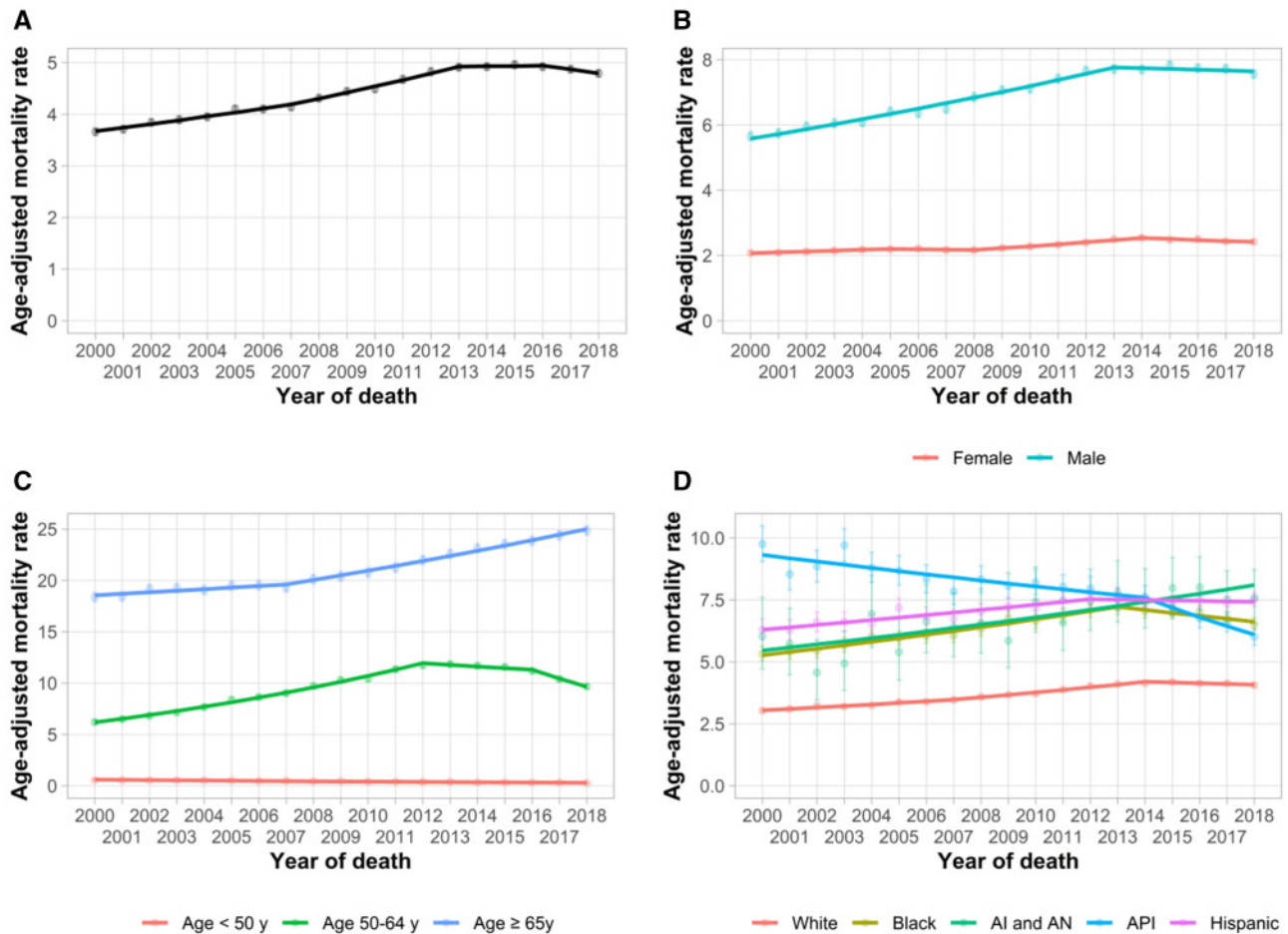
Figure 1. Age-adjusted primary liver cancer (excluding intrahepatic cholangiocarcinoma) mortality trends, 2000-2018, by sex, age, and race or ethnicity in the National Center for Health Statistics Database. **A)** Overall primary liver cancer mortality trends. **B)** Primary liver cancer mortality trends by sex. **C)** Primary liver cancer mortality trends by age. **D)** Primary liver cancer mortality trends by race or ethnicity. Error bars represent the 95% confidence intervals. AI and AN = American Indian and Alaska Native; API = Asian and Pacific Islander.

0.86-mm (95% CI = −1.10 to −0.62 mm, P < .001) decrease in the median diameter of the largest tumor per year (Figure 3, B), with a median diameter of 56.0 mm in 2004 and 48.5 mm in 2016; this trend was also seen in most subgroups (Supplementary Table 2, available online). Despite improvements in localized tumor detection, the proportion of patients receiving potentially curative treatment did not change over time (−0.08%, 95% CI = −0.45% to 0.29%, P = .66).

Trends of OS for HCC Patients in the United States

Overall 1-, 3-, and 5-year OS rates were 50.9% (95% CI = 50.6% to 51.3%), 27.6 % (95% CI = 27.2% to 27.9%), and 19.4 % (95% CI = 19.1% to 19.8%), respectively, across the study period (Table 2). OS was higher in younger patients, females, and APIs, whereas it was worse in Blacks. State-level variation was seen in OS, with 5-year OS being 57% higher in Alaska (25.6%, 95% CI = 17.7% to 37.2%) than in Louisiana (16.3%, 95% CI = 15.0% to 17.7%).

From 2000 to 2015, there were increases in 1-, 3-, and 5-year OS rates (Figure 4, A). One-year OS increased from 36.3% (95% CI = 34.3% to 38.3%) to 58.1% (95% CI = 56.9% to 59.4%) during 2000-2015, and the 5-year OS rate almost doubled from 11.7% (95% CI = 10.4% to 13.1%) to 21.3% (95% CI = 20.2% to 22.4%)

during 2000-2011. Improvement in survival was more notable in individuals with localized HCC (Figure 4, B) than those with regional (Figure 4, C) or distant HCC (Figure 4, D). Similarly, substantial improvement in OS was noted among individuals receiving curative treatments (Figure 4, E) and noncurative treatments (Figure 4, F).

In multivariable Cox regression analysis, year of diagnosis (adjusted hazard ratio = 0.96 per year, 95% CI = 0.96 to 0.97 per year, P < .001) was independently associated with OS (Table 3). With HCC patients diagnosed in 2000 as a reference group, individuals diagnosed with HCC in 2015 had a 41% decreased risk of death (adjusted hazard ratio = 0.59, 95% CI = 0.57 to 0.61, P < .001), with similar trends observed in all the subgroups (Figure 5). In addition to the year of diagnosis, male sex, older age, Black race, regional or distant stage, lack of curative treatment, and particular states were associated with poor OS (Table 3).

Discussion

In this study, we investigated the temporal trends of primary liver cancer mortality (excluding iCCA) and tumor burden at presentation, receipt of curative treatment, and OS of HCC in the United States. Despite earlier projections of rising liver
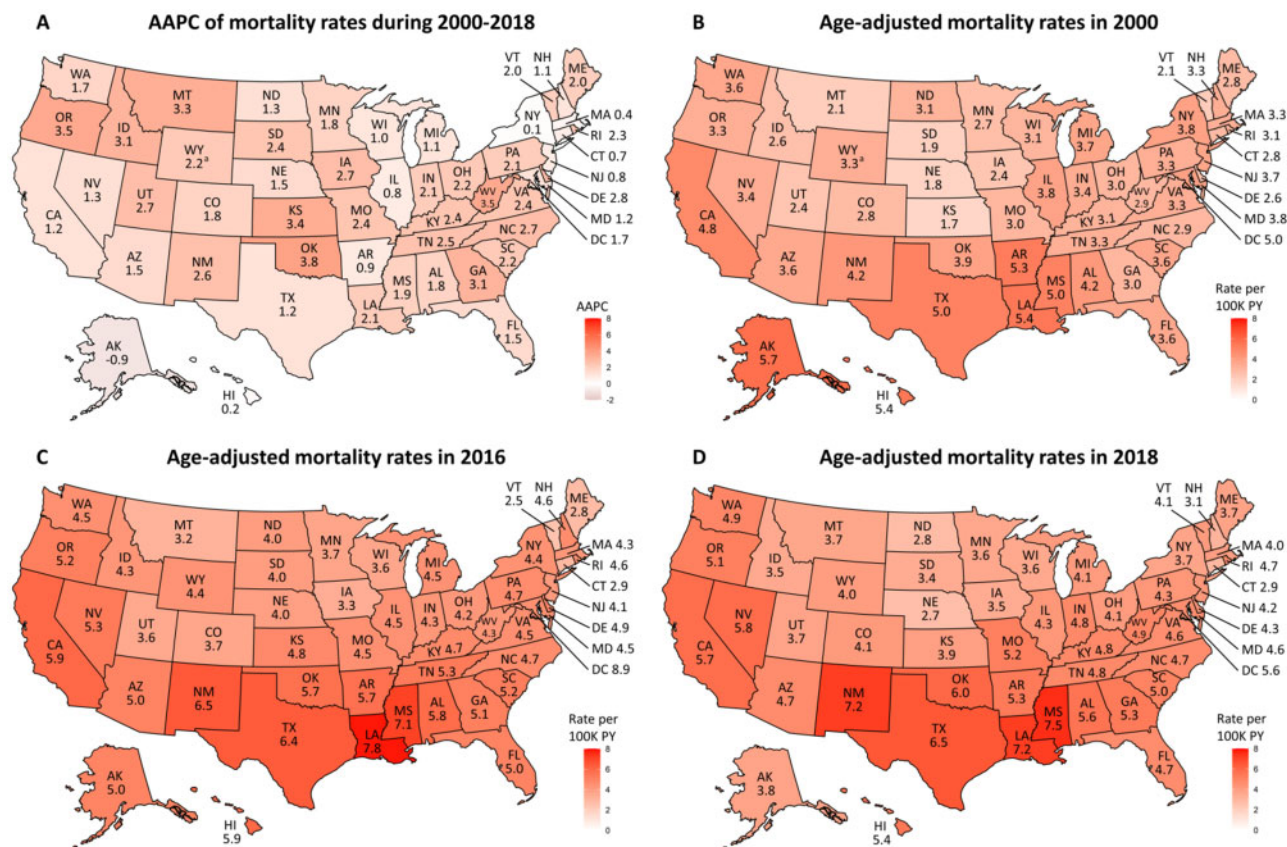
Figure 2. State-specific age-adjusted primary liver cancer mortality rates (excluding intrahepatic cholangiocarcinoma) and average annual percentage changes (AAPC) during 2000-2018 in National Center for Health Statistics Database. **A)** State-specific AAPC of primary liver cancer mortality rates during 2000-2018. **B)** State-specific mortality rates of primary liver cancer in 2000. **C)** State-specific mortality rates of primary liver cancer in 2016. **D)** State-specific mortality rates of primary liver cancer in 2018. [a]Indicates age-adjusted mortality rate in 2000 were not available. Earliest reported mortality rate was 2001 in WY, which was used to calculate AAPC in (A) and map 2000 mortality rates in (B). PY = person-years.

cancer mortality over the next decade (8), we demonstrated for the first time, to our knowledge, that liver cancer mortality rates have recently plateaued and begun to decline in the United States. Similar to recent changes in HCC incidence, we observed differences by age, race or ethnicity, and geography. Most notably, mortality rates appear to be decreasing in individuals aged younger than 65 years but continued to increase in individuals aged 65 years and older and AIs and ANs. The changes in liver cancer mortality have occurred concurrently with improvements in early tumor detection and increased OS among patients with HCC.

Compared with the recently reported 2.1% AAPC of liver cancer mortality during 1999-2016 (21), we found a lower AAPC of 1.5% with continued follow-up through 2018. Although mortality rates of liver cancer increased over the entire study period, they recently plateaued and have now started showing a downward trend. These changes likely reflect recently observed decreases in HCC incidence (4,22). For example, increased antiviral treatment programs for chronic hepatitis in the United States was reported to be associated with statistically significant reductions in HCC incidence (23-25). Studies have even demonstrated potential benefit of antiviral treatment in patients with a history of HCC given improvement in liver dysfunction (26,27). Our results showed that HCC mortality reduction is most notable in API, likely due to the effectiveness of HBV vaccination and antivirals to curve down the incidence of

HBV-associated HCC and improved liver function in patients with HBV-associated HCC (2,28,29). Outside of antiviral treatment reducing HCC mortality, we also noted improved OS among HCC patients, afforded by increased early detection and improved posttreatment outcomes.

We noted increasing mortality in individuals aged 65 years and older. This could be due to increasing burden of chronic liver disease or cirrhosis associated with metabolic syndrome, which is an important risk factor for HCC especially in elderly individuals (30). One other subgroup in whom mortality rates continue to increase and are now the highest is among AIs and ANs. Our recent study showed HCC incidence rates also continue to rise only in AIs and ANs, which likely contributed to the rising HCC mortality rate in this group (22). Higher disease burden of HCV, diabetes and metabolic syndrome in AIs and ANs as well as lower rates of screening and access to HCV treatment and hepatology care due to the socioeconomic and cultural barriers are the main drivers of the increasing burden of HCC (31,32). Similarly, incidence rates of HCC remain high in Hispanics, likely attributed to the growing burden of metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) in this population (22). Finally, we also found Black-White disparities, with Black patients having the worst OS (33). This survival disparity may be partly driven by differences in tumor stage and receipt of curative treatment, although many other patient-, provider-, and system-level interrelated factors, including

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Table 2. HCC stage, median tumor size, proportion of curative treatment receipt, and OS rate, by sex, age, race or ethnicity, and state in SEER 18 Database

Characteristic	2000-2016 (n = 74 610) Tumor stage[a]			2004-2016 (n = 64 285)	2000-2016 (n = 74 610)	2000-2015 (n = 68 876) OS rates		
	Localized, % (95% CI)	Regional, % (95% CI)	Distant, % (95% CI)	Median tumor size, cm (95% CI)[a]	Proportion of receiving curative Tx, % (95% CI)[a]	1-y OS, % (95% CI)	3-y OS, % (95% CI)	5-y OS, % (95% CI)
Overall	56.8 (56.5 to 57.2)	29.1 (28.7 to 29.4)	14.1 (13.8 to 14.4)	5.0 (5.0 to 5.0)	27.0 (26.7 to 27.3)	50.9 (50.6 to 51.3)	27.6 (27.2 to 27.9)	19.4 (19.1 to 19.8)
Sex								
Male	55.1 (54.7 to 55.5)	30.2 (29.8 to 30.6)	14.7 (14.4 to 15.0)	5.1 (5.1 to 5.1)	26.3 (25.9 to 26.6)	50.1 (49.7 to 50.5)	26.8 (26.4 to 27.2)	18.8 (18.4 to 19.1)
Female	62.5 (61.7 to 63.2)	25.5 (24.9 to 26.2)	12.0 (11.5 to 12.5)	4.7 (4.6 to 4.8)	29.4 (28.8 to 30.1)	53.5 (52.7 to 54.2)	30.2 (29.4 to 30.9)	21.6 (20.9 to 22.3)
Age, y								
<50	51.9 (50.6 to 53.1)	30.6 (29.4 to 31.8)	17.5 (16.6 to 18.5)	5.8 (5.6 to 6.0)	32.6 (31.5 to 33.8)	52.9 (51.7 to 54.2)	33.2 (32.0 to 34.4)	26.7 (25.6 to 27.9)
50-64	56.8 (56.3 to 57.3)	29.6 (29.2 to 30.1)	13.6 (13.2 to 13.9)	4.5 (4.4 to 4.5)	28.9 (28.5 to 29.4)	53.7 (53.2 to 54.3)	30.9 (30.4 to 31.4)	23.0 (22.5 to 23.5)
≥65	58.0 (57.4 to 58.6)	28.0 (27.5 to 28.6)	14.0 (13.6 to 14.4)	5.6 (5.5 to 5.7)	23.4 (23.0 to 23.9)	46.9 (46.3 to 47.5)	22.0 (21.5 to 22.5)	13.0 (12.6 to 13.5)
Race or ethnicity[a]								
Non-Hispanic White	57.0 (56.5 to 57.5)	28.9 (28.4 to 29.4)	14.1 (13.7 to 14.5)	4.8 (4.8 to 4.9)	28.1 (27.7 to 28.6)	49.9 (49.4 to 50.4)	26.6 (26.1 to 27.1)	18.9 (18.4 to 19.3)
Non-Hispanic Black	52.2 (51.2 to 53.3)	30.8 (29.8 to 31.7)	17.0 (16.2 to 17.8)	5.4 (5.3 to 5.5)	22.5 (21.7 to 23.3)	45.7 (44.7 to 46.7)	22.6 (21.7 to 23.5)	14.7 (13.9 to 15.6)
Non-Hispanic, AI and AN	54.9 (51.3 to 58.5)	33.1 (29.8 to 36.6)	12.0 (9.8 to 14.5)	5.6 (5.5 to 5.7)	23.7 (20.9 to 26.6)	50.2 (46.9 to 53.8)	27.5 (24.4 to 31.0)	17.6 (14.8 to 21.0)
Non-Hispanic, API	57.5 (56.6 to 58.4)	29.4 (28.6 to 30.2)	13.1 (12.5 to 13.7)	4.8 (4.5 to 5.1)	32.5 (31.7 to 33.3)	56.7 (55.8 to 57.5)	35.0 (34.1 to 35.9)	25.7 (24.9 to 26.6)
Hispanic	59.0 (58.1 to 59.9)	27.9 (27.1 to 28.7)	13.1 (12.5 to 13.7)	4.8 (4.7 to 4.8)	22.3 (21.7 to 23.0)	51.9 (51.1 to 52.8)	26.5 (25.7 to 27.4)	18.0 (17.3 to 18.8)
State								
Alaska	55.6 (45.2 to 65.5)	30.3 (21.5 to 40.4)	14.1 (8.0 to 22.6)	4.6 (3.9 to 5.4)	40.0 (30.6 to 50.0)	59.1 (50.2 to 69.6)	34.2 (25.6 to 45.7)	25.6 (17.7 to 37.2)
California	57.5 (57.0 to 58.0)	29.0 (28.5 to 29.5)	13.5 (13.2 to 13.9)	5.0 (5.0 to 5.0)	25.2 (24.7 to 25.6)	52.8 (52.3 to 53.3)	28.7 (28.2 to 29.2)	19.9 (19.4 to 20.4)
Connecticut	57.8 (55.9 to 59.7)	28.5 (26.8 to 30.2)	13.7 (12.4 to 15.0)	4.6 (4.4 to 4.7)	34.5 (32.8 to 36.3)	53.5 (51.7 to 55.3)	29.6 (27.9 to 31.4)	20.1 (18.5 to 21.9)
Georgia	54.1 (52.8 to 55.4)	30.5 (29.3 to 31.7)	15.4 (14.4 to 16.3)	5.3 (5.1 to 5.4)	24.0 (22.9 to 25.1)	46.8 (45.5 to 48.1)	24.3 (23.1 to 25.5)	17.5 (16.4 to 18.7)
Hawaii	56.0 (53.5 to 58.4)	31.1 (28.8 to 33.5)	12.9 (11.3 to 14.7)	5.8 (5.5 to 6.0)	37.9 (35.6 to 40.2)	52.1 (49.7 to 54.5)	29.7 (27.5 to 32.1)	20.5 (18.4 to 22.7)
Iowa	51.0 (48.5 to 53.4)	34.9 (32.6 to 37.3)	14.1 (12.5 to 15.9)	5.1 (4.9 to 5.4)	23.0 (21.0 to 25.0)	47.8 (45.5 to 50.3)	25.5 (23.3 to 27.8)	18.7 (16.7 to 21.0)
Kentucky	56.3 (54.4 to 58.2)	28.7 (27.0 to 30.4)	15.0 (13.7 to 16.4)	5.2 (5.0 to 5.4)	30.5 (28.8 to 32.1)	45.6 (43.8 to 47.4)	24.6 (23.0 to 26.3)	17.1 (15.6 to 18.7)
Louisiana	57.3 (55.7 to 58.8)	27.5 (26.1 to 28.9)	15.3 (14.1 to 16.4)	5.3 (5.1 to 5.4)	24.6 (23.3 to 26.0)	44.5 (42.9 to 46.1)	21.8 (20.4 to 23.3)	16.3 (15.0 to 17.7)
Michigan	54.9 (53.2 to 56.6)	29.2 (27.7 to 30.8)	15.9 (14.7 to 17.2)	5.0 (4.8 to 5.2)	30.6 (29.0 to 32.1)	47.1 (45.4 to 48.8)	26.1 (24.6 to 27.7)	18.5 (17.1 to 20.0)
New Jersey	57.4 (56.1 to 58.7)	26.3 (25.2 to 27.4)	16.3 (15.3 to 17.3)	5.0 (4.9 to 5.1)	31.0 (29.9 to 32.1)	50.2 (49.1 to 51.5)	27.7 (26.6 to 28.8)	20.5 (19.4 to 21.6)
New Mexico	62.1 (59.7 to 64.4)	22.5 (20.5 to 24.6)	15.5 (13.7 to 17.3)	5.2 (5.0 to 5.4)	20.1 (18.3 to 21.9)	47.5 (45.3 to 49.9)	23.9 (21.8 to 26.1)	16.7 (14.8 to 18.8)
Utah	57.8 (54.7 to 60.8)	29.9 (27.2 to 32.8)	12.3 (10.4 to 14.5)	4.9 (4.6 to 5.2)	28.3 (25.7 to 31.1)	49.7 (46.8 to 52.8)	28.0 (25.3 to 31.1)	20.0 (17.4 to 23.0)
Washington	55.6 (54.1 to 57.1)	32.9 (31.5 to 34.3)	11.5 (10.6 to 12.5)	4.4 (4.3 to 4.6)	31.6 (30.2 to 32.9)	55.0 (53.5 to 56.4)	30.7 (29.3 to 32.2)	21.8 (20.4 to 23.2)

[a] Percents were calculated after excluding missing data for race or ethnicity (0.2%), tumor size (17.3%), tumor stage (8.9%), and treatment modality (0.9%). AI and AN = American Indian and Alaska Native; API = Asian and Pacific Islander; CI = confidence interval; HCC = hepatocellular carcinoma; OS = overall survival; SEER = Surveillance, Epidemiology, and End Results; Tx = treatment.
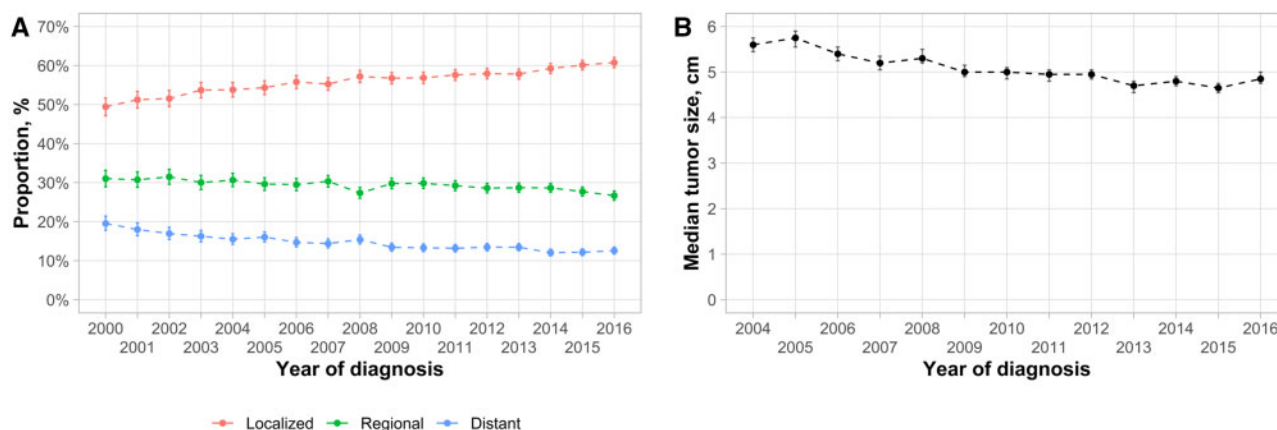
Figure 3. Trends of hepatocellular carcinoma (HCC) tumor stages (2000-2016) and median tumor sizes (2004-2016) in Surveillance, Epidemiology, and End Results 18 Database. **A)** Trends of HCC tumor stages during 2000-2016. **B)** Trends of median tumor sizes during 2004-2016. Error bars represent the 95% confidence intervals.

patient barriers to medical care, issues of medical mistrust, and provider implicit bias, likely contribute to survival disparity in Blacks (34,35). Although tumor growth biology and growth patterns can differ between patients, existing data do not suggest differences in tumor biology by race or ethnicity, suggesting disparities are more related to health-care delivery factors (36). The result highlights the urgency of targeted interventions and resource allocation to prevent liver cancer mortality among racial or ethnic minorities.

Several studies have reported improving early detection and OS in HCC patients in recent years (5,37). Indeed, our study also showed considerable improvement in OS, especially in HCC patients with localized disease. The increased proportion of localized HCC and decreased median size of tumors indicate the role of surveillance and early diagnosis as a determinant of improving prognosis (38,39).

The improved survival among HCC patients receiving curative and noncurative treatments and the year of diagnosis as an independent prognostic factor suggests that refinement of HCC treatment allocation and efficacy likely contribute to improvements in survival as well. This is consistent with the fact that the treatment allocation algorithm for HCC has been revolutionized during the past 2 decades (6,40). For example, surgical technique, perioperative management, and patient selection for HCC resection have all improved (41). Liver transplant organ allocation policy and selection of appropriate candidates have improved for HCC patients, which led to an excellent long-term outcome with very low risk of posttransplant cancer recurrence (42). Technical improvement and candidate selection for transarterial chemoembolization led to a decreased risk of post-transarterial chemoembolization liver failure and local tumor progression (43). Finally, there were improvements in cirrhosis management over the same time period, especially in HCC patients with viral hepatitis-induced liver cirrhosis (26). Although the survival improvement for patients with advanced HCC is not as obvious as for those with localized or regional disease, we did observe a substantial increase in 1-year survival. This survival improvement could be related to the approval of sorafenib as the first systemic therapy for advanced HCC in 2008 (44,45). With continued advances in therapy for advanced HCC (2,46,47), it is expected the prognosis of patients with advanced HCC will also continue to improve rapidly in the next 3-5 years.

We also noted state-level variations in liver cancer mortality, tumor stage, receipt of curative treatment, and OS. Higher liver cancer mortality states are clustered in the southern US, although it is unclear if this is simply related to higher incidence rates, higher prevalence of risk factors (eg, obesity, diabetes), and/or other geographic disparities in early detection and treatment receipt. Future studies should investigate the causes of this geographic disparity to inform future intervention strategies.

We acknowledge there are some limitations to analyzing the large cancer registry data database. First of all, the database does not provide data regarding underlying liver disease etiology or other granular clinical data, including receipt of viral hepatitis treatment and liver disease severity, which is an important prognostic factor in patients with HCC. In addition, the SEER Program records the staging information using SEER Summary Stage 2000 across the study period instead of the commonly used Barcelona Clinic Liver Cancer staging system, which not only considers tumor burden but also incorporates liver function and patient performance status. We reported primary liver cancer mortality excluding iCCA to estimate HCC mortality in our main analysis because mortality statistics specific for HCC are not available in the NCHS database (9). However, our sensitivity analysis showed that liver cancer mortality excluding iCCA in the entire United States closely mirrors the HCC mortality trend in the SEER 18 database, which is representative of the general population covering approximately 28% of the United States (12). Finally, the tumor extent specific variable, treatment, and survival data were not available in the NCHS database (9); thus, we used the SEER 18 database to investigate the temporal trends of tumor extent at diagnosis, treatment, and OS. It should be noted that there could still be variation in the management and outcome of HCC in the remaining 72% of the US population that are not represented in the SEER 18 registries.

In conclusion, the mortality of primary liver cancer appears to have plateaued and started downtrending. In addition to decreasing incidence, increased early HCC detection and advances in treatment allocation and efficacy likely contributed to observed decreases in mortality. It is expected that the prognosis of patients with HCC will continue to improve with the advent of novel curative, locoregional, and systemic treatments. Future studies should further investigate the underlying causes of
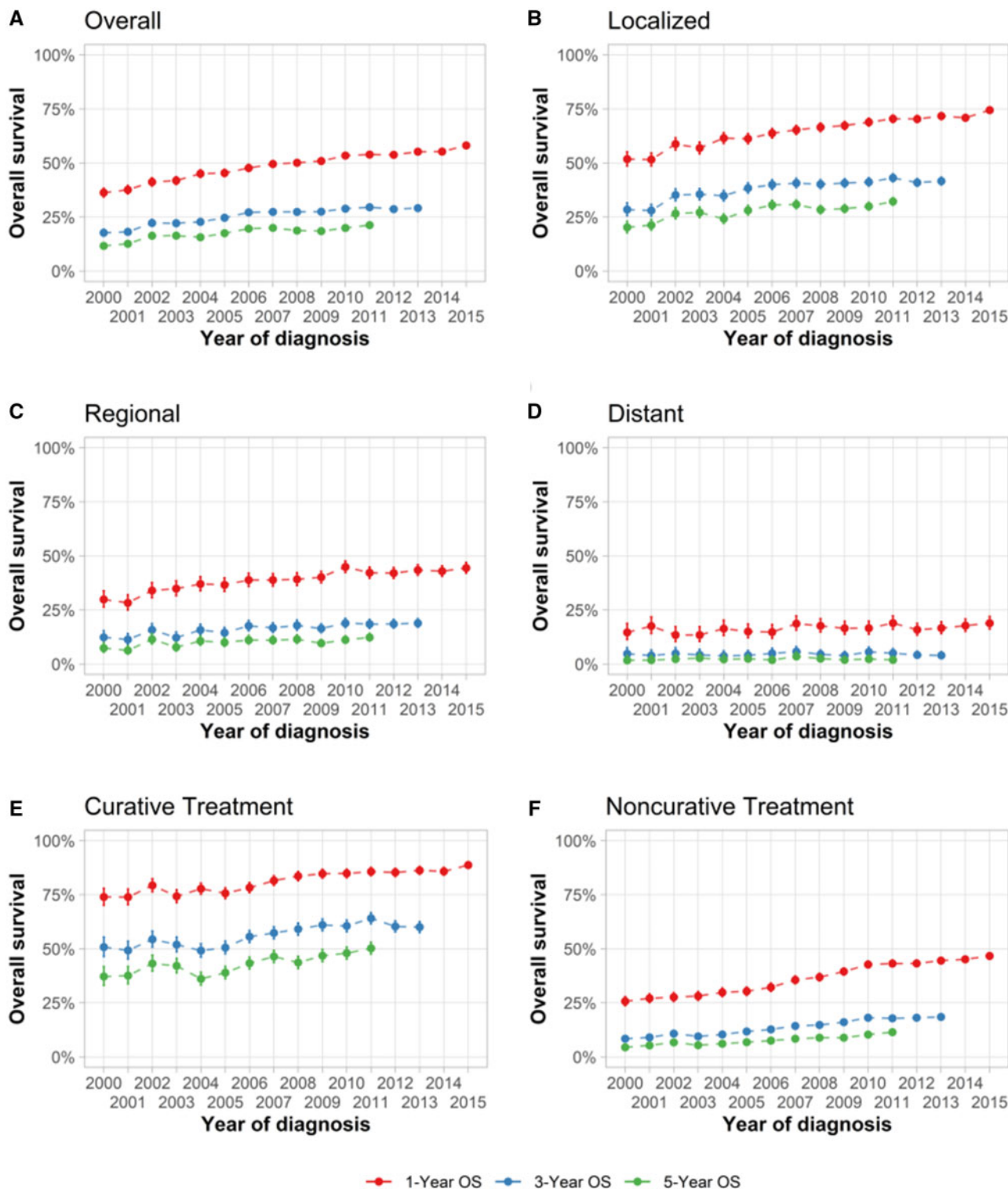
Figure 4. Trends of 1-, 3-, 5-year overall survival (OS) of hepatocellular carcinoma (HCC) patients by tumor stages and receipt of curative treatments in Surveillance, Epidemiology, and End Results 18 Database. **A)** Trends of 1-, 3-, and 5-year OS of overall HCC patients. **B)** Trends of 1-, 3-, and 5-year OS of HCC patients with localized disease. **C)** Trends of 1-, 3-, and 5-year OS of HCC patients with regional disease. **D)** Trends of 1-, 3-, and 5-year OS of HCC patients with distant disease. **E)** Trends of 1-, 3-, and 5-year OS of HCC patients receiving curative treatment. **F)** Trends of 1-, 3-, and 5-year OS of HCC patients receiving noncurative treatment. Error bars represent the 95% confidence intervals.

Table 3. Univariate and multivariable Cox proportional hazards model assessing factors associated with HCC overall survival in SEER 18 Database

Characteristics	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P	aHR (95% CI)	P
Year of diagnosis, per year	0.97 (0.97 to 0.97)	<.001	0.96 (0.96 to 0.97)	<.001
Sex				
Female	Ref	Ref	Ref	Ref
Male	1.10 (1.08 to 1.12)	<.001	1.09 (1.07 to 1.11)	<.001
Age, per 10 y	1.16 (1.15 to 1.17)	<.001	1.15 (1.14 to 1.16)	<.001
Race or ethnicity[a]				
Non-Hispanic White	Ref	Ref	Ref	Ref
Non-Hispanic Black	1.14 (1.11 to 1.17)	<.001	1.10 (1.07 to 1.13)	<.001
Non-Hispanic AI and AN	1.00 (0.92 to 1.08)	1.00	1.04 (0.96 to 1.13)	.35
Non-Hispanic API	0.81 (0.79 to 0.83)	<.001	0.82 (0.79 to 0.84)	<.001
Hispanic	0.98 (0.96 to 1.00)	.08	1.00 (0.97 to 1.02)	.72
State				
California	Ref	Ref	Ref	Ref
Alaska	0.84 (0.67 to 1.06)	.15	0.88 (0.68 to 1.13)	.32
Connecticut	1.00 (0.95 to 1.04)	.82	1.03 (0.99 to 1.08)	.18
Georgia	1.15 (1.11 to 1.18)	<.001	1.13 (1.09 to 1.17)	<.001
Hawaii	1.03 (0.98 to 1.09)	.24	1.32 (1.24 to 1.39)	<.001
Iowa	1.09 (1.03 to 1.15)	.003	1.06 (1.01 to 1.12)	.03
Kentucky	1.16 (1.11 to 1.21)	<.001	1.26 (1.21 to 1.32)	<.001
Louisiana	1.21 (1.17 to 1.26)	<.001	1.21 (1.17 to 1.26)	<.001
Michigan	1.10 (1.06 to 1.15)	<.001	1.13 (1.08 to 1.17)	<.001
New Jersey	1.03 (1.00 to 1.06)	.04	1.02 (0.99 to 1.06)	.16
New Mexico	1.15 (1.09 to 1.21)	<.001	1.11 (1.05 to 1.17)	<.001
Utah	1.04 (0.97 to 1.12)	.24	1.13 (1.05 to 1.21)	<.001
Washington	0.95 (0.91 to 0.98)	.002	1.06 (1.02 to 1.10)	.001
Stage[a]				
Localized	Ref	Ref	Ref	Ref
Regional	2.01 (1.97 to 2.05)	<.001	1.64 (1.60 to 1.67)	<.001
Distant	4.02 (3.92 to 4.12)	<.001	2.57 (2.50 to 2.64)	<.001
Treatment modality[a]	—	—	—	—
Noncurative treatment	Ref	Ref	Ref	Ref
Curative treatment	0.30 (0.29 to 0.30)	<.001	0.35 (0.34 to 0.36)	<.001

[a]Missing data for race or ethnicity (0.2%), tumor stage (8.9%), and treatment modality (0.9%) were imputed as described in the Methods section. aHR = adjusted hazard ratio; AI and AN = American Indian and Alaska Native; API = Asian and Pacific Islander; CI = confidence interval; HCC = hepatocellular carcinoma; HR = hazard ratio; SEER = Surveillance, Epidemiology, and End Results.

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demographic and state-level variation in liver cancer mortality and outcome. Finally, targeted interventions and resource allocation are needed to minimize HCC disparities in the United States.

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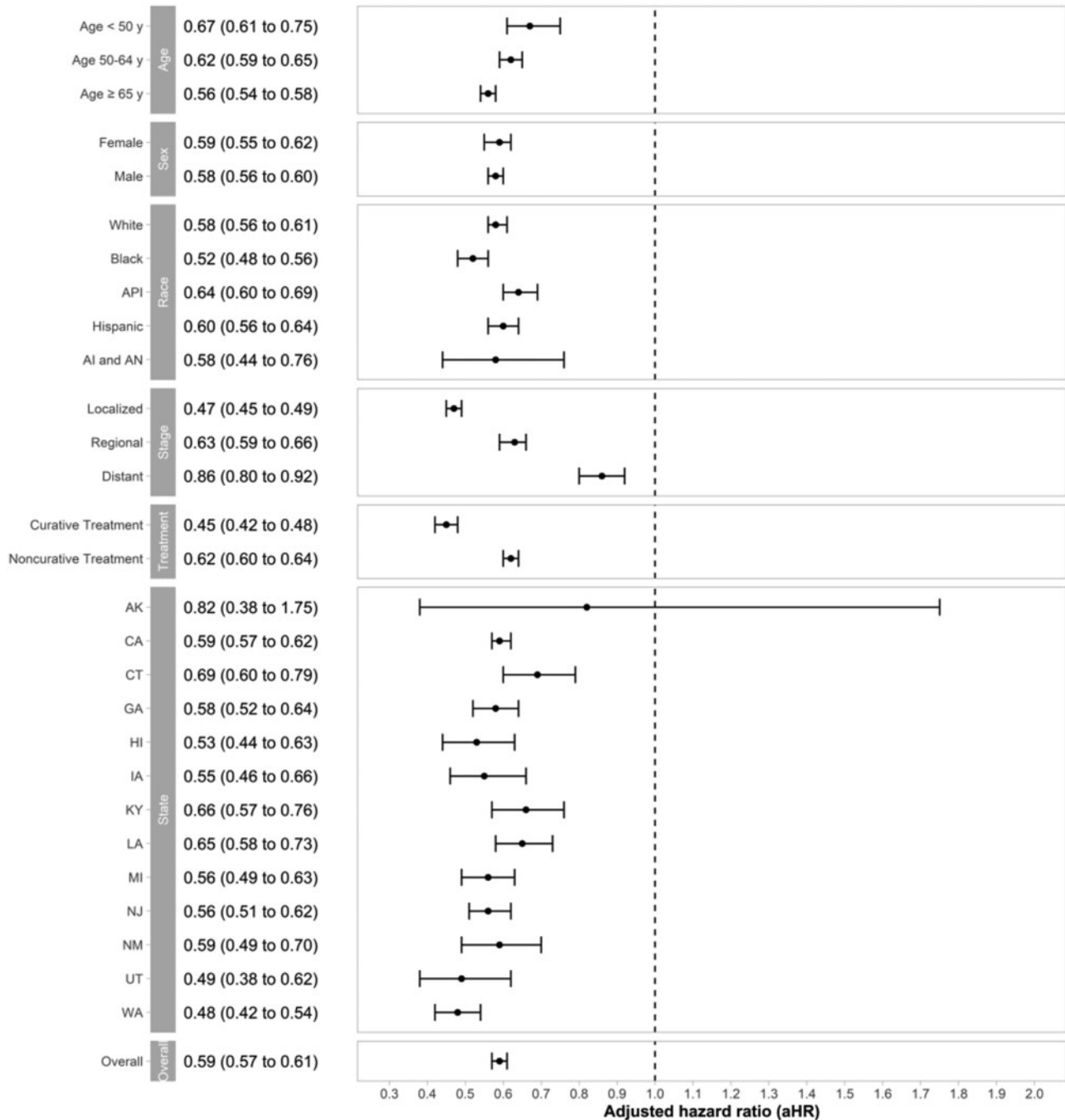
Figure 5. Improvement in overall survival of hepatocellular carcinoma (HCC) diagnosed in 2015 compared with HCC diagnosed in 2000 in Surveillance, Epidemiology, and End Results 18 Database. Adjusted hazard ratio of the diagnosis year 2015 with the diagnosis year of 2000 as a reference group. Error bars represent the 95% confidence intervals.

Data Availability

The data underlying this article are available in NCHS Database: Mortality—All COD, Aggregated With State, Total U.S. (1990-2018) <Katrina/Rita Population Adjustment> and SEER 18 Database: Incidence-Based Mortality—SEER Research Data, 18 Registries, Nov 2019 Sub (2000-2017) at https://seer.cancer.gov/data/access.html, and can be accessed with Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat).

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