Gastroenterology 2021;160:1140–1150

CLINICAL—LIVER

County Differences in Liver Mortality in the United States: Impact of Sociodemographics, Disease Risk Factors, and Access to Care

David Goldberg,[1] Katherine Ross-Driscoll,[2,3] and Raymond Lynch[3]

[1]Division of Digestive Health and Liver Diseases, Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida; [2]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia; and [3]Division of Transplantation, Department of Surgery, Emory University School of Medicine, Atlanta, Georgia

BACKGROUND AND AIMS: Data have demonstrated state-wide variability in mortality rates from liver disease (cirrhosis + hepatocellular carcinoma), but data are lacking at the local level (eg, county) to identify factors associated with variability in liver disease–related mortality and hotspots of liver disease mortality. **METHODS:** We used Centers for Disease Control and Prevention's Wide-ranging Online Data for Epidemiologic Research data from 2009 to 2018 to calculate county-level, age-adjusted liver disease–related death rates. We fit multivariable linear regression models to adjust for county-level covariates related to demographics (ie, race and ethnicity), medical comorbidities (eg, obesity), access to care (eg, uninsured rate), and geographic (eg, distance to closest liver transplant center) variables. We used optimized hotspot analysis to identify clusters of liver disease mortality hotspots based on the final multivariable models. **RESULTS:** In multivariable models, 61% of the variability in among-county mortality was explained by county-level race/ethnicity, poverty, uninsured rates, distance to the closest transplant center, and local rates of obesity, diabetes, and alcohol use. Despite adjustment, significant within-state variability in county-level mortality rates was found. Of counties in the top fifth percentile (ie, highest mortality) of fully adjusted mortality, 60% were located in 3 states: Oklahoma, Texas, and New Mexico. Adjusted mortality rates were highly spatially correlated, representing 5 clusters: South Florida; Appalachia and the eastern part of the Midwest; Texas and Oklahoma; New Mexico, Arizona, California, and southern Oregon; and parts of Washington and Montana. **CONCLUSIONS:** Our data demonstrate significant intrastate differences in liver disease–related mortality, with more than 60% of the variability explained by patient demographics, clinical risk factors for liver disease, and access to specialty liver care.

Keywords: Liver Mortality; Chronic Liver Disease; Hepatocellular Carcinoma; Cirrhosis.

Liver disease represents a worsening concern for American patients and clinicians. The number of annual deaths from cirrhosis in the United States increased by 65% between 1999 and 2016, whereas deaths from hepatocellular carcinoma (HCC) doubled during this same period.[1] Deaths rates from liver-related disease (cirrhosis and HCC) increased in 49 of 50 states, with disproportionate increases in 5 states (Alabama, Arkansas, Indiana, Kentucky, and New Mexico).[1] The most notable trends in liver disease–related mortality were increased rates among younger people (ages 25–34); Whites, Native Americans, and Hispanics; and patients with alcohol-related liver disease.[1] However, these data were only evaluated at the state level, even though variations in socioeconomic conditions and healthcare infrastructure within a given state may be associated with more local mortality differences. A 2016 study in *JAMA* demonstrated county-level differences in mortality from cirrhosis and chronic liver disease; however, the range in county-level mortality from liver disease was the smallest of the 10 diseases studied.[2] In contrast to study by Tapper and Parikh,[1] this study did not include HCC deaths in the cirrhosis and chronic liver disease category, even though >90% of cases of HCC occur in the setting of cirrhosis/advanced fibrosis, and did not account for data in the era of direct-acting antiviral therapy for hepatitis C virus (HCV).[1–9] Additionally, neither of these studies explored the impact of sociodemographic factors and measures of access to care (eg, insurance, proximity to a liver transplant center) on geographic variability in liver disease–related mortality.

Clinicians seeking to develop interventions to address modifiable factors leading to geographic disparities in liver disease–related mortality require data on a more local level to identify hotspots of liver disease. At the same time, policymakers can leverage data on local differences in liver disease–related mortality and the impact of measures of access to care (eg, proximity to a transplant center) to develop policies to help remediate disparities in liver disease–related mortality across the United States (eg, opening new transplant centers, enhancing provision of telehealth coverage).[10,11] In this analysis, we sought to quantify county-level differences in liver disease–related mortality and to assess the determinants of variability in mortality using national liver mortality data.

Methods

Study Outcome

The primary outcome was county-level, age-adjusted liver disease–related mortality among adults aged 25–74 years from using diagnosis codes for chronic liver disease (including

Abbreviations used in this paper: CDC WONDER, Centers for Disease Control and Prevention's Wide-ranging Online Data for Epidemiologic Research; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2020.11.016

WHAT YOU NEED TO KNOW

BACKGROUND & CONTEXT

Data are lacking at the 'local' (eg, county) level to identify factors associated with variability in liver disease-related mortality and hotspots of liver disease mortality.

NEW FINDINGS

In multivariable models, 61% of the variability in among-county mortality was explained by county-level race/ethnicity, poverty, uninsured rates, distance to the closest transplant center, and local rates of obesity, diabetes, and alcohol use. Despite adjustment, there was significant within-state variability in county-level mortality rates.

LIMITATIONS

The analysis relied on county-, rather than individual patient-level data.

IMPACT

Our study identifies potential modifiable risk factors to mitigate county-level mortality from liver disease (eg, increase access to specialty care) and hotspots of liver disease mortality in the US.

HCC) from the Centers for Disease Control and Prevention's Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) platform. Because data suggest that relying only on diagnosis codes for alcoholic liver disease (K70), chronic hepatitis (K73), and fibrosis and cirrhosis (K74) can lead to an underestimation of liver disease–related mortality,[12] we sought to balance our inclusionary International Classification of Diseases, 10th revision codes to capture as many liver disease–related deaths as possible, without including too many "garbage codes" (Supplementary Table 1).[13] We believe this maximized the most accurate capture of liver disease–related mortality and was more expansive than the only other study evaluating county-level differences in mortality from liver disease that did not include HCC in the grouping of liver disease–related mortality, even though >90% of deaths occur in the setting of advanced and/or chronic liver disease.[1,2,14]

Study Period

We focused on liver disease–related deaths between 2009 and 2018. We included aggregated survival data from 2009 to 2018 because CDC WONDER does not provide age-adjusted data on counties with fewer than 20 deaths because these age-adjusted rates are considered unreliable. Therefore, we sought to maximize the number of counties to evaluate in multivariable models. Secondarily, we divided the cohort into pre–direct-acting antiviral (2009–2013) and post–direct-acting antiviral (2014–2018) eras to evaluate temporal trends in county-level liver disease–related mortality.

County-level Covariates

We considered potential covariates that may be associated with liver disease–related mortality for a given individual (eg, diabetes) or for everyone residing in a county (eg, distance to a specialized center).[15–20] However, all these measures were assessed at the county level because data were not available at the patient level: (1) rural or urban status based on classification from the US Census Bureau[21]; (2) poverty defined as percentage of adult population living below the federal poverty level in 2013 based on the Small Area Income and Poverty Estimates Program[22]; (3) race and ethnicity using population estimates from the US Census Bureau in CDC WONDER[23,24]; (4) uninsured rate, defined as the mean annual percentage from 2009 to 2018 without health insurance based on the Small Area Health Insurance Estimates Program[25]; (5) distance from geographic centroid to closest liver transplant center; (6) number of board-certified gastroenterologists per adult population in 2015 using data from the Area Health Resources Files[26]; (7) local transplant wait-listing rates from 2009 to 2018 (calculated as the number of wait-listings per county per 100 liver disease deaths)[15]; (8) percentage of adults with "heavy" drinking (consumption, on average, of more than 1 drink per day for women or 2 drinks per day for men in the past 30 days) from 2009 to 2012[14]; (9) percentage of adults with diabetes from 2009 to 2012[27]; and (10) percentage of adults classified as obese in 2011.[28]

Statistical Analysis

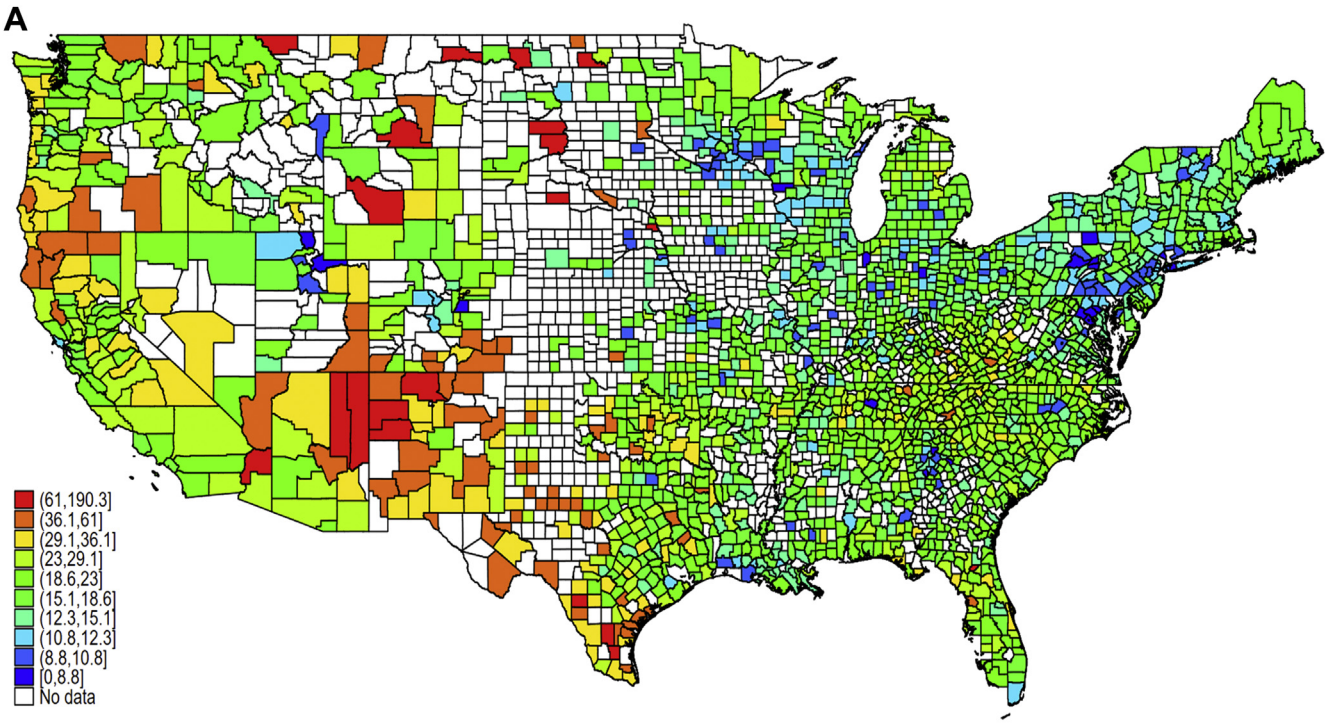
Ascertainment of age-adjusted mortality. Age-adjusted liver disease mortality rates (primary outcome) were obtained from CDC WONDER, using methodology described in detail at https://wonder.cdc.gov/wonder/help/ucd.html.[24] In short, age-adjusted death rates are calculated by the "direct method" using the year "2000 US standard" as the default population.[24] CDC WONDER provided age-adjusted rates by county aggregated over 2009–2018 for the primary analysis and for 2009–2013 and 2014–2018 for the secondary analysis.

Mapping of mortality data. We mapped county-level mortality data using the *spmap* function in STATA 16.0 (StataCorp).

Linear regression models. We fit linear regression models to identify county-level factors associated with age-adjusted liver disease–related mortality. We evaluated each covariate in univariable models and used a backward selection process to include covariates with a $P < .05$ in the final model and/or covariates that increased the R^2 of the final model.

Calculation of fully adjusted mortality rates. After fitting the final multivariable linear regression models, we calculated fully adjusted, county-level liver disease–related mortality rates using the *predict* command in STATA 16.0

Geospatial hotspot analysis. The age-adjusted and fully adjusted mortality rates were used as input for cluster analysis with optimized hotspot analysis (ArcGIS Desktop, Release 10; Environmental Systems Research Institute, Redlands, CA); the distance band used for analysis was identified based on incremental spatial autocorrelation.[29,30] We considered clusters (not individual counties) statistically significant at $P < .05$ and a Z score of 1.96 (95% confidence level). An important note about clustering is that it is "high-high" clustering. Counties that are part of a hotspot might not have the highest mortality but are both higher than expected (statistically) and surrounded by other counties that are higher than expected. As a result, an individual county can be considered part of a hotspot based on its surrounding counties, even if it is not in the top 5% for mortality.[29,30]


A
(61,190.3]
(36.1,61]
(29.1,36.1]
(23,29.1]
(18.6,23]
(15.1,18.6]
(12.3,15.1]
(10.8,12.3]
(8.8,10.8]
[0,8.8]
No data

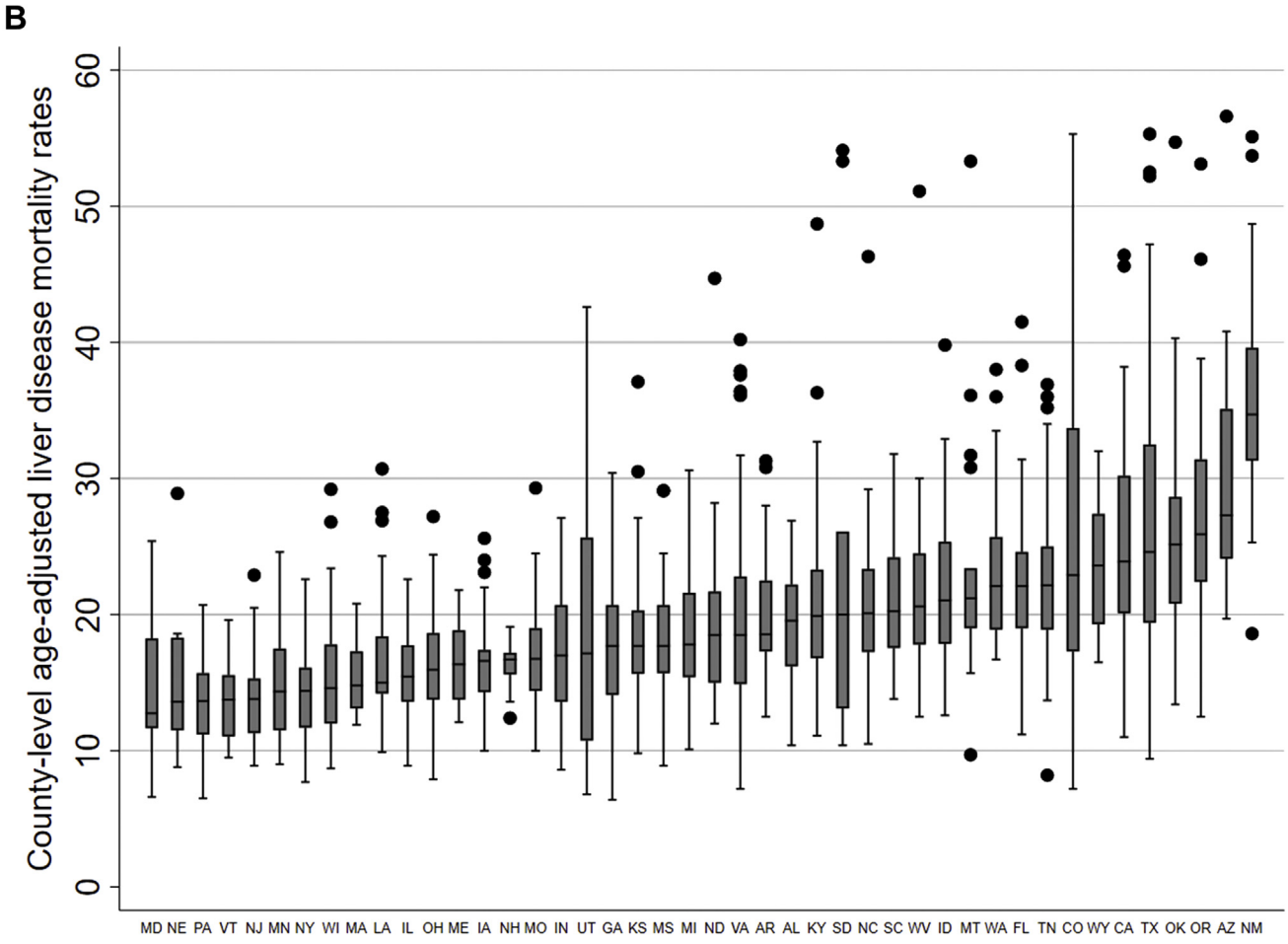

B
County-level age-adjusted liver disease mortality rates
0
10
20
30
40
50
60
MD NE PA VT NJ MN NY WI MA LA IL OH ME IA NH MO IN UT GA KS MS MI ND VA AR AL KY SD NC SC WV ID MT WA FL TN CO WY CA TX OK OR AZ NM

Table 1. Multivariable Linear Regression Model Evaluating Factors Associated With County-level Age-adjusted Liver Disease–related Mortality Rates

County-level Variable	β Coefficient	*P*	Unadjusted R^2
Racial/ethnic composition			
% White Hispanic	0.20 (0.16, 0.23)	<.001	0.08
% Black non-Hispanic	–0.10 (–0.14, –0.07)	<.001	0.008
% Black Hispanic	–0.93 (–1.65, –0.21)	.01	0.002
% Asian	–0.14 (–0.27, –0.02)	.03	0.01
% Native American	0.97 (0.91, 1.03)	<.001	0.40
% Adults living below poverty level	0.20 (0.11, 0.30)	<.001	0.11
% Uninsured	0.10 (0.02, 0.18)	.01	0.17
Miles to closest liver transplant center[a]	0.12 (0.07, 0.17)	<.001	0.08
% With diabetes	1.01 (0.70, 1.33)	<.001	0.09
% With heavy alcohol use	0.33 (0.16, 0.51)	<.001	0.002
Listings per 100 deaths	–0.05 (–0.06, –0.04)	<.001	0.09

NOTE. Model did not include county rural or urban classification, number of board-certified gastroenterologists, and percentage of county residents classified as obese because they were not associated with county-level, age-adjusted, liver disease–related mortality ($P > .1$ for all variables) and did not change the overall R^2 of the multivariable model. The β coefficients with a positive value were associated with increased county-level liver disease–related mortality. Overall R^2 of the multivariable model = 0.62.
[a]Per unit increase of 10 miles.

Ethics

The study was considered exempt by the Institutional Review Board at the University of Miami because it only included deidentified population-level data. All authors had access to the study data and reviewed and approved the final manuscript.

Results

Overall Results

From 2009 to 2018, 3125 US counties were identified by CDC WONDER.[24] Among these, only some counties (n = 314, 10.0%) had both population and liver disease deaths sufficient to allow computation of annual county age-adjusted mortality rates, hence the aggregation of data from 2009 to 2018. There were 1527 (48.9%) and 1717 (54.9%) counties with available data in the pre– and post–direct-acting antiviral eras, respectively, but 2124 (68.0%) in the overall aggregated cohort of 2009–2018, representing 97.6% of all liver disease–related deaths in the United States among the population ages 25–74 during this period.

Individual County Level

At the individual county level, the median age-adjusted liver disease death rate from 2009 to 2018 was 18.6 deaths per 100,000 population (interquartile range, 15.1–23.0). The counties with the top 5% of mortality rates (103 counties) were found in 22 different states; however, more than 40% of the counties with the highest mortality rates were located in either Texas (n = 33, 32.1%) or New Mexico (n = 12, 11.7%) (Figure 1*A*). The counties with the lowest death rates (bottom fifth percentile) were spread across 28 states and were more evenly distributed, with 13 (12.3% of total) in Pennsylvania and no other state contributing more than 6% of the total. Only 1 county (0.9%) was in Texas, and none was in New Mexico.

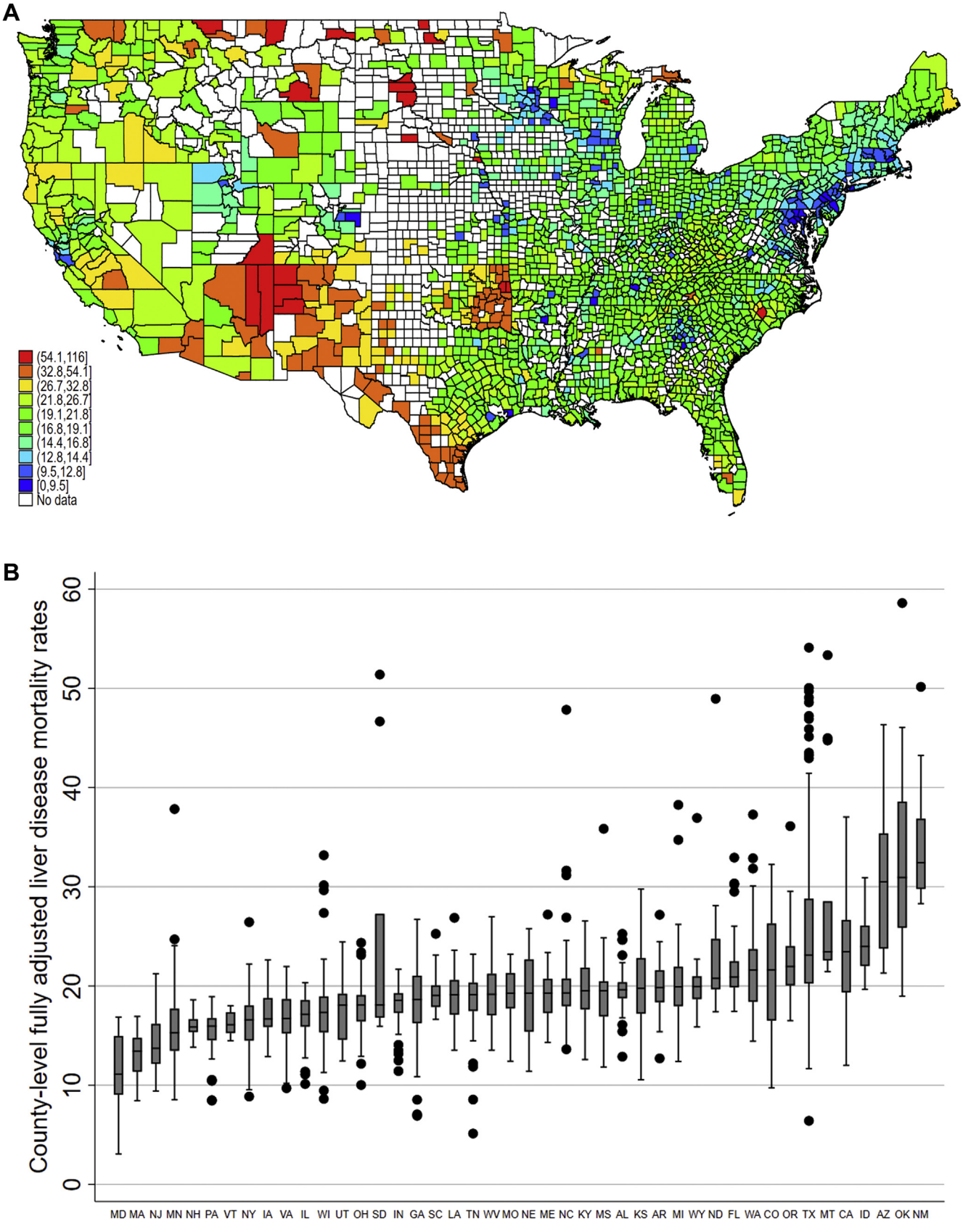
Within-state Variability in County-level Mortality

There were marked differences in the within-state, among-county, liver disease–related mortality (limited to states with at least 10 counties with available data) (Figure 1*B*). Three states (MA, ME, NH) had a less than 2-fold difference in mortality among counties with the highest and lowest mortality, whereas 3 states (NE, ND, SD) had a more than 10-fold difference (Figure 1*B*). Eight states (CO, KS, NE, SD, TN, TX, UT) had at least 1 county in the top and bottom fifth percentile of age-adjusted liver disease–related mortality from 2009 to 2018.

Multivariable Models

In univariable linear regression models, all covariates were associated with the outcome of county-level, age-adjusted, liver disease mortality rate ($P < .1$) (Supplementary Table 2). However, in multivariable linear regression models, county rural or urban classification, number of board-certified gastroenterologists, and percentage of the county population classified as obese were no longer significant ($P > .1$). Several county-level variables were significantly associated with county-specific, age-adjusted, liver disease–related mortality rates (Table 1). Those with a positive β coefficient were associated with increased adjusted county-level liver disease–related mortality (eg, counties with an increased percentage of Native American or counties located farther from a liver transplant center had higher liver disease–related mortality rates), whereas those with a negative β coefficient had lower rates of liver disease–related mortality (eg, counties with an increased percentage of black non-Hispanics had lower mortality). Together, these variables accounted for 62% of

Figure 1. County-level variability in liver disease–related mortality rates. (*A*) County-level, age-adjusted, liver disease–related mortality rates; 2009–2018. (*B*) Within-state variability in age-adjusted, county-level, liver disease–related mortality rates; 2009–2018. *CDC WONDER age-adjusted mortality rates exclude counties with fewer than 20 liver disease–related deaths because of "unreliable" age-adjusted rates. †Legend categories based on 1st, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 99th percentile of mortality. ‡The *y*-axis excludes top 1% of counties, and only states (n = 45) with 10 or more counties with available data were included.


A
(54.1,116]
(32.8,54.1]
(26.7,32.8]
(21.8,26.7]
(19.1,21.8]
(16.8,19.1]
(14.4,16.8]
(12.8,14.4]
(9.5,12.8]
[0,9.5]
No data
B
County-level fully adjusted liver disease mortality rates
0
10
20
30
40
50
60
MD MA NJ MN NH PA VT NY IA VA IL WI UT OH SD IN GA SC LA TN WV MO NE ME NC KY MS AL KS AR MI WY ND FL WA CO OR TX MT CA ID AZ OK NM

the observed proportion of variance in county-level mortality rates (Table 1, $R^2 = 0.617$). County-level liver transplant wait-listing rates were significantly associated with age-adjusted mortality rates in multivariable models and increased the R^2.

Fully Adjusted County-level Mortality Rates

Despite adjustment for the county-level variables associated with age-adjusted liver mortality rates, there was continued variability in county-level mortality rates, although this was somewhat attenuated (Figure 2*A*). The counties with fully adjusted mortality rates in the bottom fifth percentile (ie, lowest mortality) were distributed across 26 states, led by Maryland (n = 13, 12.9% of total), New York (n = 10, 9.9%), and Georgia (7.9%). In contrast, counties in the top fifth percentile (ie, highest mortality) of fully adjusted mortality encompassed 27 states, with more than 50% of them located in Texas (n = 29, 23.6%), Oklahoma (n = 25, 20.3%), and New Mexico (n = 13, 10.6%). Notably, 13 counties (50.0%) in New Mexico were in the top fifth percentile for highest fully adjusted liver disease mortality. Although there continued to be within-state, among-county differences in liver disease–related mortality after adjusting for all covariates in the multivariable model, the within-state variability was attenuated. Twelve states had a less than 2-fold difference in mortality among the counties with the highest and lowest mortality in the respective state, whereas only 2 states (SD, WI) had a more than 10-fold difference and 5 others a more than 5-fold difference (AR, NE, ND, TX, and UT) (Figure 2*B*).

Geospatial Hotspot Analysis

Adjusted mortality rates were highly spatially correlated, representing 5 distinct clusters across the United States (Figure 3*A* and *B*). The age-adjusted hotspot analysis identified statistically significant clusters of counties with high age-adjusted mortality rates from liver disease (Figure 3*A*), whereas the fully adjusted hotspot analysis identified statistically significant clusters of counties with high mortality rates from liver disease that are not explained by variation in the county population characteristics accounted for in our multivariable models (Figure 3*B*). Statistically significant hotspots were identified that encompassed South Florida; Appalachia and the eastern part of the Midwest (fully adjusted hotspot analysis extended through all of Michigan and far eastern Wisconsin); Texas and Oklahoma; New Mexico, Arizona, California, and southern Oregon; and parts of Washington and Montana. Notably, these areas had significantly higher than expected mortality from liver disease even after adjusting for factors that might traditionally explain this relationship, such as population composition and socioeconomic status, in the multivariable linear regression model, even if individual counties in the cluster did not have the highest mortality (eg, Broward County in South Florida was at the 54th percentile for mortality).

Temporal Trends

There were 1337 counties (42.8% of all counties and 62.9% of the counties in the 2011–2018 analysis) with sufficient data in both the 2009–2013 and 2014–2018 periods. Among those 1337 counties, 984 (73.6%) had a higher age-adjusted mortality rate in 2014–2018 compared with 2009–2013, of which 773 counties had a relative increase in the age-adjusted mortality rate of ≥10% and 426 with a relative increase in the age-adjusted mortality rate of ≥25% (Figure 4). Conversely, 158 counties had a relative decrease in the age-adjusted mortality rate of ≥10% and 42 counties a relative decrease of ≥25% (Figure 4). Of the 42 counties (across 22 states) with the greatest relative decrease in age-adjusted liver disease–related mortality, only 20 were in a state that expanded Medicaid under the Affordable Care Act in 2014, whereas 22 were in states that did not expand during the study period (TX, 6; GA, 3; NC, 3; VA, 3; FL, ID, KS, MS, OK, SC, and WI, 1 each).

Discussion

Using 10 years of county-level mortality data, we demonstrated substantial local variability in liver disease–related mortality rates, with 5 geographic clusters of mortality in the United States. Although prior studies have shown state-level differences in mortality from cirrhosis and HCC and county-level differences from cirrhosis and chronic liver disease–related mortality (excluding HCC), these studies did not evaluate differences in mortality from all liver disease (cirrhosis + HCC) at the local level, did not examine the population-level sociodemographic and geographic variables contributing to the local variability in liver disease–related mortality, and did not perform formal hotspot analyses.[1,2] Our data highlight that county-level racial composition and socioeconomic conditions (eg, poverty, insurance) and remoteness from specialty care together account for nearly 60% of the variance in county-level mortality. These data have important public health and policy implications that help to identify hotspots of liver disease–related mortality not explained by the sociodemographic characteristics of the population and require further study and interventions to help mitigate these disparities.

Our findings are consistent with state-level data published in 2018.[1] The age-adjusted liver disease mortality rates differed across the 50 states, and the temporal changes

Figure 2. County-level variability in liver disease–related mortality rates. (*A*) County-level, fully adjusted, liver disease–related mortality rates; 2009–2018. (*B*) Within-state variability in fully adjusted, county-level, liver disease–related mortality rates; 2009–2018. *CDC WONDER age-adjusted mortality rates exclude counties with fewer than 20 liver disease–related deaths because of "unreliable" age-adjusted rates. †Legend categories based on 1st, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 99th percentile of mortality. ‡The *y*-axis excludes top 1% of counties, and only states (n = 46) with 10 or more counties with available data were included. **Fully adjusted mortality rates based on postestimation predictions of multivariable linear regression models. Legend categories based on 1st, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 99th percentile of mortality.

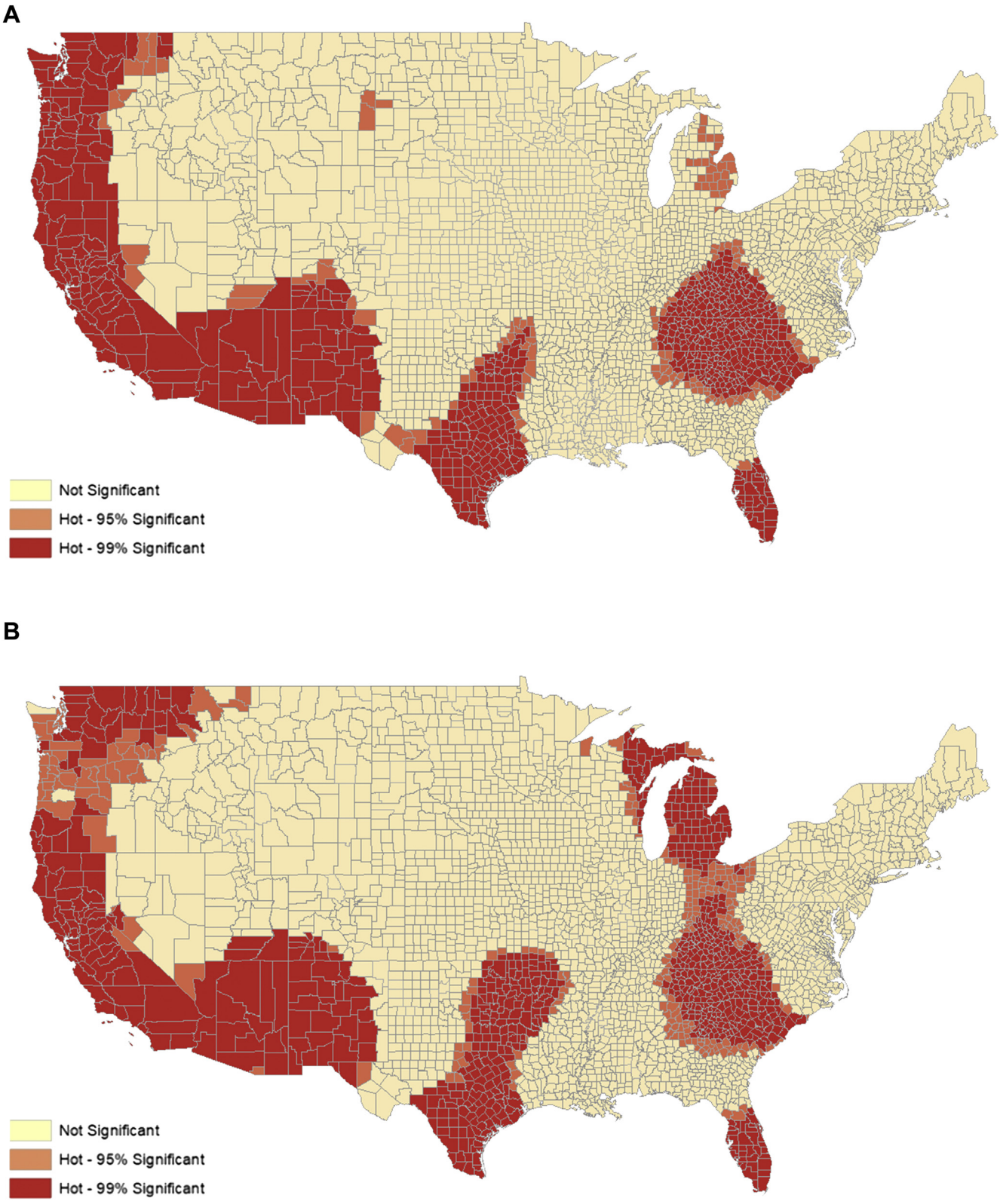


Figure 3. Geospatial hotspot analysis of liver disease–related mortality from 2009 to 2018. (*A*) Geospatial hotspot analysis based on age-adjusted liver disease–related mortality rates. (*B*) Geospatial hotspot analysis based on fully adjusted liver disease–related mortality rates. *Hotspot analysis identifies clusters with significantly increased mortality based on county-level *Z* scores and *P* values ($P < .05$ and $P < .01$). †Mortality rates based on fully adjusted liver disease–related mortality from multivariable linear regression model.

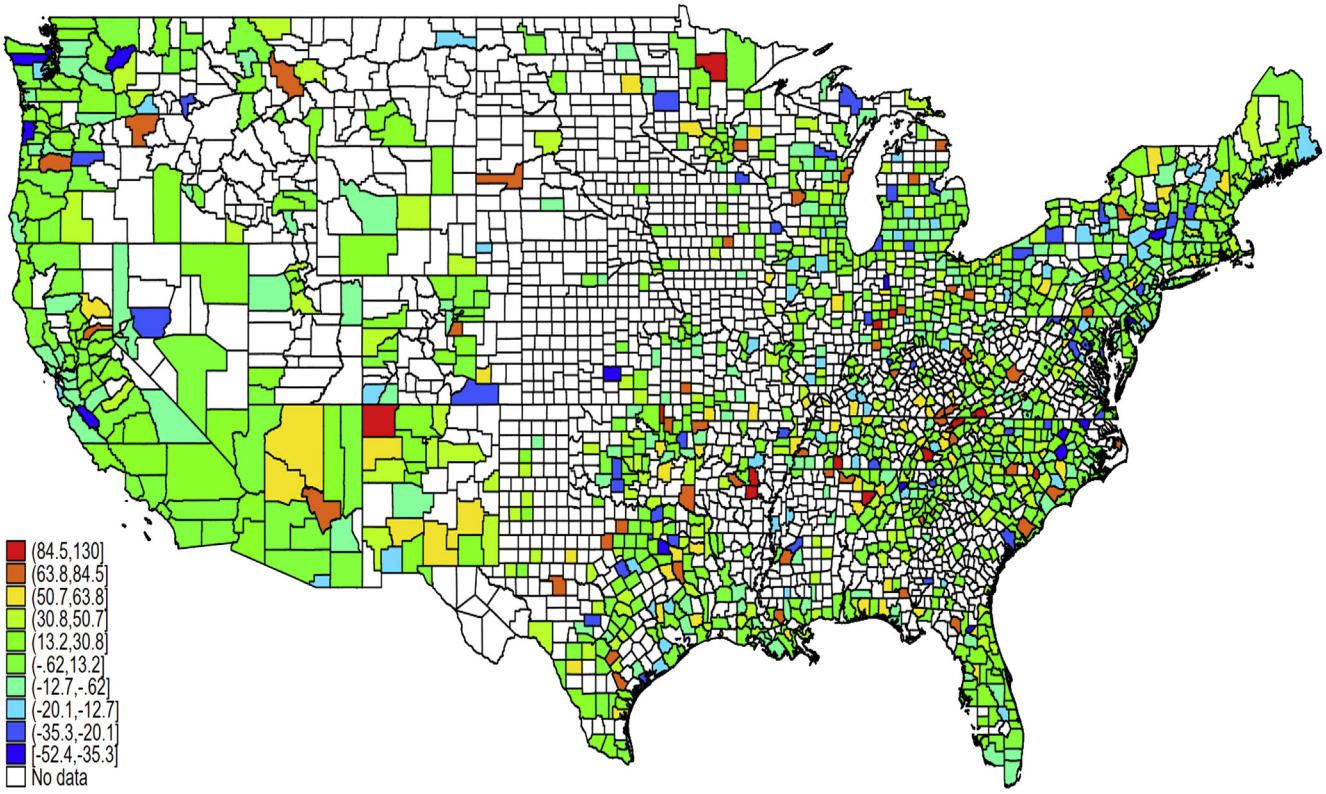


Figure 4. Relative percentage of change in county-level, age-adjusted, liver disease–related mortality from 2009–2013 to 2014–2018. Map includes data on 1472 counties with ≥20 liver disease–related deaths in both time periods.

in liver disease mortality were not uniform across the United States. Most notably, mortality rates increased the most in the South and West of the United States.[1] Furthermore, this previous work identified differences in liver disease mortality across specific populations (eg, Native Americans). The range in mortality across counties seen in our study is similar to that from an analysis of cirrhosis and chronic liver disease–related mortality published in 2016.[2] That study demonstrated a difference of 14.0 deaths per 100,000 population between the 90th and 10th percentile counties (25.5 vs 11.5), whereas we found a difference of 16.8 deaths per 100,000 population (29.1 vs 12.3).[2] The difference in results is attributable to our study including HCC in the grouping of liver disease–related mortality, given that >90% of deaths occur in the setting of advanced and/or chronic liver disease.[1,2,14] Tapper and Parikh[2] found that the difference in age-standardized cirrhosis and chronic liver disease–related mortality in the 90th vs 10th percentile counties in 2014 was the smallest among the 10 diseases they studied. In contrast to the Tapper and Parikh study,[2] this study did not include HCC deaths in the cirrhosis and chronic liver disease category, even though >90% of cases of HCC occur in the setting of cirrhosis/advanced fibrosis and did not account for data in the era of direct-acting antiviral therapy for HCV.[1–6] Neither of these studies, however, explored the determinants of the variability in liver disease mortality rates. By focusing on county-level data, we demonstrated significant differences in mortality among counties within the same state and specific hotspots of liver disease mortality even after accounting for important county-level sociodemographic and access to care variables.

The within-state variability in mortality we demonstrated differed across the United States, with some states having little variability and others having a more than 10-fold difference in age-adjusted liver disease–related mortality. In addition, beyond demographics, we identified important measures of access to care that help to explain nearly 60% of the variance in county-level mortality, although other factors (eg, rates of HCV, access to primary care) may explain the residual variance. It is also important to note that the covariates in our model were examined at the county rather than patient level and therefore must be interpreted differently from a typical model using patient-level data. The data on race must also be interpreted in a similar fashion, although prior studies have shown lower rates of mortality from cirrhosis in blacks.[1] However, other variables that apply to all residents of a county, notably distance (or rurality), can be interpreted similarly to a model with patient-level data because the covariate applies the same to everyone in that geographic area.

Although prior studies have demonstrated that mortality rates for many chronic diseases are higher for those living in rural areas, including heart disease, cancer, stroke, chronic respiratory disease, and even HCC, our study found that rurality was not significant but rather distance to a transplant center was significantly associated with county-level mortality rates.[1,5,20,31–41] However, those prior studies

focused only on rural or urban status rather than proximity to specialty care, which is important in patients with cirrhosis and HCC, who have significantly lower mortality when they are treated by hepatology specialists who almost exclusively practice at a liver transplant center.[16–18,31,42–45] The association between distance to a transplant center and liver disease–related survival on a population level validates published data from our group showing that increased distance from a transplant center, rather than rurality, is associated with increased mortality among Veterans with end-stage liver disease[16] and commercially insured patients with decompensated cirrhosis and/or HCC.[17] However, even after accounting for distance and other county-level variables, we identified 5 geographic hotspots of liver disease–related mortality that cannot be explained solely by the variables in our model.

Mortality may be higher in these areas because of factors that we could not account for in our model (eg, prevalence of HCV, access to primary care, or other socioeconomic, cultural, and/or biologic factors in the population for which we could not fully adjust).[46] Nevertheless, several policy and care initiatives could be considered based on these findings. First, efforts to enhance telehealth coverage and outreach are needed for geographically isolated patients, which has been shown to improve care and survival for patients with HCV[47–56] and to improve access to transplantation for patients with end-stage liver disease.[57] Second, data on county-level mortality and distance to a liver transplant center could better inform decisions when opening new liver transplant center(s), a strategy that has been proposed in other countries, or at the minimum satellite clinics to provide liver care to those with the highest mortality rates.[10] Third, these county-level data can be used to apply area-need variables to promote equitable distribution of transplant grafts based on the perspective of mortality of the broader population with end-stage liver disease.[58]

Our analyses demonstrated that counties with a higher percentage of uninsured patients had higher liver disease–related mortality rates. Differential access to insurance under the Affordable Care Act, both in terms of lower-cost health insurance through healthcare exchanges and Medicaid for states that expanded Medicaid, may have impacted both county- and state-level mortality rates. It is possible expanded access to health insurance could help to remediate disparities in counties with low uninsured rates. However, to fully address this requires a difference-in-difference analysis that evaluates changes in mortality across states as a function of Medicaid expansion, which is beyond the scope of this article.

Our study did have limitations. First, because of the small number of liver disease–related deaths in many counties in any individual year, we combined 10 years of data for the primary analyses. Although there have been temporal changes in mortality, the results of our multivariable model are unlikely to have been biased by aggregation of 10 years of data. Second, we evaluated mortality and potential explanatory variables in aggregate at the county-level because of a lack of patient-level data for mortality and exposures. Although this does not allow us to conclude if individual factors are associated with mortality at the patient level (eg, obesity), several variables are uniform across the county (eg, distance), and the goal was to evaluate geographic differences in mortality at a county level. Third, we were unable to evaluate local rates of specific diseases (eg, HCV). Additionally, death certificate data have substantial missingness related to the underlying cause of liver disease (eg, in 2018 <10% of the deaths had a diagnosis of HCV or non-alcoholic steatohepatitis in the CDC dataset), and therefore we could not evaluate for temporal changes in the cause of liver disease–related deaths. Although these factors may have explained the differences in mortality we found (eg, certain counties have higher prevalence of HCV and therefore higher rates of liver disease–related mortality), they would have been mediators in the causal pathway rather than confounders to be adjusted for in models. Fourth, certain variables were not available for the entire study period (eg, obesity, drinking), although this is unlikely to have biased our findings substantially. Finally, we are unable to evaluate local factors that may explain the striking mortality differences in the same state (eg, Oklahoma), and this identifies a research future direction to obtain more granular data to evaluate factors influencing differences in mortality in the same geographic area. Ultimately, the limitations of the data do not allow us to conclude whether the higher mortality rates in certain hotspots is due to a higher prevalence of liver disease, more severe/aggressive cases, poor access to care, substandard care, or a combination of these factors. These analyses, which would be stratified by key variables, require a different data source that is not constrained by CDC limitations of reporting data for areas with a small number of deaths (<20) for a given group of interest. Additionally, county-level data may obscure local, neighborhood-level disparities that cannot be addressed using these data. Also, we cannot address the potential beneficial (or detrimental) effect of movement from 1 area to another on an individual's risk of liver disease–related mortality. Therefore, further work is needed to explore these issues.

In conclusion, our data clearly demonstrate significant intrastate differences in liver disease–related mortality and several sociodemographic and access to care variables that help to explain this variability. These data help to identify hotspots of liver disease while identifying potentially modifiable factors (eg, proximity to a liver transplant center) that could help to remediate observed disparities, including improving access to specialized liver care. Further studies are needed to examine interplay of these factors and to identify other variables that contribute to the substantial county-level differences in liver disease–related mortality.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org and at https://doi.org/10.1053/j.gastro.2020.11.016.

References

1. Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999–2016: observational study. BMJ 2018;362:k2817.
2. Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, et al. US county-level trends in mortality rates for major causes of death, 1980–2014. JAMA 2016;316:2385–2401.
3. Xiang X, You XM, Zhong JH, Li LQ. Hepatocellular carcinoma in the absence of cirrhosis in patients with chronic hepatitis B virus infection. J Hepatol 2017;67:885–886.
4. Mittal S, El-Serag HB, Sada YH, et al. Hepatocellular carcinoma in the absence of cirrhosis in united states veterans is associated with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2016;14:124–131.
5. El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011;365:1118–1127.
6. Shah SA, Smith JK, Li Y, Ng SC, Carroll JE, Tseng JF. Underutilization of therapy for hepatocellular carcinoma in the Medicare population. Cancer 2011;117:1019–1026.
7. Backus LI, Belperio PS, Shahoumian TA, Mole LA. Direct-acting antiviral sustained virologic response: impact on mortality in patients without advanced liver disease. Hepatology 2018;68:827–838.
8. Backus LI, Belperio PS, Shahoumian TA, Mole LA. Impact of sustained virologic response with direct-acting antiviral treatment on mortality in patients with advanced liver disease. Hepatology 2019;69:487–497.
9. Belperio PS, Shahoumian TA, Loomis TP, Mole LA, Backus LI. Real-world effectiveness of daclatasvir plus sofosbuvir and velpatasvir/sofosbuvir in hepatitis C genotype 2 and 3. J Hepatol 2019;70:15–23.
10. Webb GJ, Hodson J, Chauhan A, et al. Proximity to transplant center and outcome among liver transplant patients. Am J Transplant 2019;19:208–220.
11. Arora S, Thornton K, Murata G, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. N Engl J Med 2011;364:2199–2207.
12. Asrani SK, Larson JJ, Yawn B, Therneau TM, Kim WR. Underestimation of liver-related mortality in the United States. Gastroenterology 2013;145:375–382.
13. Naghavi M, Makela S, Foreman K, O'Brien J, Pourmalek F, Lozano R. Algorithms for enhancing public health utility of national causes-of-death data. Popul Health Metr 2010;8:9.
14. Dwyer-Lindgren L, Flaxman AD, Ng M, Hansen GM, Murray CJ, Mokdad AH. Drinking patterns in US counties from 2002 to 2012. Am J Public Health 2015;105:1120–1127.
15. Lynch RJ, Ye F, Sheng Q, Zhao Z, Karp SJ. State-based liver distribution: broad sharing with less harm to vulnerable and underserved communities compared with concentric circles. Liver Transplant 2019;25:588–597.
16. Goldberg DS, French B, Forde KA, et al. Association of distance from a transplant center with access to waitlist placement, receipt of liver transplantation, and survival among US veterans. JAMA 2014;311:1234–1243.
17. Goldberg DS, Newcomb C, Gilroy R, et al. Increased distance to a liver transplant center is associated with higher mortality for patients with chronic liver failure. Clin Gastroenterol Hepatol 2017;15:958–960.
18. Ross K, Patzer RE, Goldberg DS, Lynch RJ. Sociodemographic determinants of waitlist and posttransplant survival among end-stage liver disease patients. Am J Transplant 2017;17:2879–2889.
19. Ross KH, Patzer RE, Goldberg D, Osborne NH, Lynch RJ. Rural-urban differences in in-hospital mortality among admissions for end-stage liver disease in the United States. Liver Transplant 2019;25:1321–1332.
20. Cross SH, Mehra MR, Bhatt DL, et al. Rural-urban differences in cardiovascular mortality in the US, 1999–2017. JAMA 2020;323:1852–1854.
21. US Census Bureau. Urban and rural. Available at: https://www.census.gov/programs-surveys/geography/guidance/geo-areas/urban-rural.html. Accessed July 28, 2020.
22. US Census Bureau. Small Area Income and Poverty Estimates (SAIPE) program. Available at: https://www.census.gov/programs-surveys/saipe.html. Accessed July 9, 2020.
23. US Department of Health and Human Services. Centers for Disease Control and Prevention. National Center for Health Statistics. The validity of race and Hispanic-origin reporting on death certificates in the United States: an update. Available at: https://www.cdc.gov/nchs/data/series/sr_02/sr02_172.pdf. Accessed July 28, 2020.
24. Centers for Disease Control and Prevention. Underlying cause of death 1999–2018. Available at: https://wonder.cdc.gov/wonder/help/ucd.html#. Accessed July 28, 2020.
25. US Census Bureau. Small Area Health Insurance Estimates (SAHIE). Available at: https://www.census.gov/content/census/en/programs-surveys/sahie.html/. Accessed July 7, 2020.
26. HRSA area health resources files. Available at: https://data.hrsa.gov/topics/health-workforce/ahrf. Accessed July 26, 2020.
27. Institute for Health Metrics and Evaluation. Diagnosed and undiagnosed diabetes prevalence by county in the U.S., 1999–2012. Seattle, WA: Institute for Health Metrics and Evaluation, 2016.
28. Institute for Health Metrics and Evaluation. Life expectancy, physical activity, and obesity by county in the U.S., 2001–2011. Seattle, WA: Institute for Health Metrics and Evaluation, 2016.
29. Patel RS, Walker T, Weber ZT, Kelley SD, Hansen R. A pilot study using geospatial analysis to identify hot-spot of populations utilizing services at university based counseling centers [published online ahead of print July 28, 2020]. J Amer Coll Health. https://doi.org/10.1080/07448481.2020.1798970.
30. Hernandez A, Branscum AJ, Li J, MacKinnon NJ, Hincapie AL, Cuadros DF. Epidemiological and geospatial profile of the prescription opioid crisis in Ohio, United States. Sci Rep 2020;10:4341.
31. Centers for Disease Control and Prevention. Potentially excess deaths from the five leading causes of death in metropolitan and nonmetropolitan counties — United States, 2010–2017. Available at: https://www.cdc.gov/mmwr/volumes/68/ss/ss6810a1.htm?s_cid=ss6810a1_w. Accessed August 3, 2020.
32. Blake KD, Moss JL, Gaysynsky A, Srinivasan S, Croyle RT. Making the case for investment in rural cancer control: an analysis of rural cancer incidence, mortality,

and funding trends. Cancer Epidemiol Biomark Prevent 2017;26:992–997.
33. Hoehn RS, Hanseman DJ, Jernigan PL, et al. Disparities in care for patients with curable hepatocellular carcinoma. HPB 2015;17:747–752.
34. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–1022.
35. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012;379:1245–1255.
36. Artinyan A, Mailey B, Sanchez-Luege N, et al. Race, ethnicity, and socioeconomic status influence the survival of patients with hepatocellular carcinoma in the United States. Cancer 2010;116:1367–1377.
37. Mathur AK, Osborne NH, Lynch RJ, Ghaferi AA, Dimick JB, Sonnenday CJ. Racial/ethnic disparities in access to care and survival for patients with early-stage hepatocellular carcinoma. Arch Surg 2010;145:1158–1163.
38. Stewart SL, Kwong SL, Bowlus CL, et al. Racial/ethnic disparities in hepatocellular carcinoma treatment and survival in California, 1988–2012. World J Gastroenterol 2016;22:8584–8595.
39. Altekruse SF, Henley SJ, Cucinelli JE, McGlynn KA. Changing hepatocellular carcinoma incidence and liver cancer mortality rates in the United States. Am J Gastroenterol 2014;109:542–553.
40. Xu L, Kim Y, Spolverato G, Gani F, Pawlik TM. Racial disparities in treatment and survival of patients with hepatocellular carcinoma in the United States. Hepatobil Surg Nutr 2016;5:43–52.
41. Rich NE, Hester C, Odewole M, et al. Racial and ethnic differences in presentation and outcomes of hepatocellular carcinoma. Clin Gastroenterol Hepatology 2019;17:551–559.
42. Cicalese L, Shirafkan A, Jennings K, Zorzi D, Rastellini C. Increased risk of death for patients on the waitlist for liver transplant residing at greater distance from specialized liver transplant centers in the United States. Transplantation 2016;100:2146–2152.
43. Patwardhan V, Paul S, Corey KE, et al. Hepatocellular carcinoma screening rates vary by etiology of cirrhosis and involvement of gastrointestinal sub-specialists. Dig Dis Sci 2011;56:3316–3322.
44. Bini EJ, Weinshel EH, Generoso R, et al. Impact of gastroenterology consultation on the outcomes of patients admitted to the hospital with decompensated cirrhosis. Hepatology 2001;34:1089–1095.
45. Kanwal F, Kramer JR, Buchanan P, et al. The quality of care provided to patients with cirrhosis and ascites in the Department of Veterans Affairs. Gastroenterology 2012;143:70–77.
46. Nguyen GC, Thuluvath PJ. Racial disparity in liver disease: biological, cultural, or socioeconomic factors. Hepatology 2008;47:1058–1066.
47. Page K, Qeadan F, Qualls C, Thornton K, Arora S. Project ECHO revisited: propensity score analysis and HCV treatment outcomes. Hepat Med 2019;11:149–152.
48. Mohsen W, Chan P, Whelan M, et al. Hepatitis C treatment for difficult to access populations: can telementoring (as distinct from telemedicine) help? Intern Med J 2019;49:351–357.
49. Mendizabal M, Ridruejo E, Ceballos S, et al. The ECHO model proved to be a useful tool to increase clinicians' self-effectiveness for care of patients with Hepatitis C in Argentina. J Viral Hepatitis 2019;26:1284–1292.
50. Marciano S, Haddad L, Plazzotta F, et al. Implementation of the ECHO(®) telementoring model for the treatment of patients with hepatitis C. J Med Virol 2017;89:660–664.
51. Jayasekera CR, Arora S, Ahmed A. Hepatitis C treatment delivery mandates optimizing available health care human resources: a case for task shifting. JAMA 2016;315:1947–1948.
52. Dhiman RK, Grover GS, Premkumar M, et al. Decentralized care with generic direct-acting antivirals in the management of chronic hepatitis C in a public health care setting. J Hepatol 2019;71:1076–1085.
53. Arora S, Thornton K, Jenkusky SM, Parish B, Scaletti JV. Project ECHO: linking university specialists with rural and prison-based clinicians to improve care for people with chronic hepatitis C in New Mexico. Public Health Rep 2007;122(Suppl 2):74–77.
54. Arora S, Thornton K. Novel models of hepatitis C virus care delivery: telemedicine, project ECHO, and integrative care. Clin Liver Dis 2020;16:5–7.
55. Arora S, Kalishman S, Thornton K, et al. Expanding access to hepatitis C virus treatment—Extension for Community Healthcare Outcomes (ECHO) project: disruptive innovation in specialty care. Hepatology 2010;52:1124–1133.
56. Arora S, Kalishman S, Dion D, et al. Partnering urban academic medical centers and rural primary care clinicians to provide complex chronic disease care. Health Aff (Millwood) 2011;30:1176–1184.
57. John BV, Love E, Dahman B, et al. Use of telehealth expedites evaluation and listing of patients referred for liver transplant. Clin Gastroenterol Hepatol 2020;18:1822–1830.
58. Goldberg DS, French B, Sahota G, Wallace AE, Lewis JD, Halpern SD. Use of population-based data to demonstrate how waitlist-based metrics overestimate geographic disparities in access to liver transplant care. Am J Transplant 2016;16:2903–2911.

Received August 11, 2020. Accepted November 10, 2020.

Correspondence
Address correspondence to: David Goldberg, MD, MSCE, University of Miami Miller School of Medicine, Don Soffer Clinical Research Building, 1120 NW 14th Street, Office no. 807, Miami, FL 33136. e-mail: dsgoldberg@med.miami.edu.

CRediT Authorship Contributions
David Goldberg, MD, MSCE (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Investigation: Lead; Methodology: Lead; Project administration: Lead; Resources: Lead; Software: Lead; Writing – original draft: Lead; Writing – review & editing: Lead).
Katherine Ross-Driscoll, MPH (Conceptualization: Supporting; Data curation: Supporting; Formal analysis: Supporting; Writing – original draft: Supporting; Writing – review & editing: Supporting).
Raymond Lynch, MD (Conceptualization: Supporting; Data curation: Supporting; Formal analysis: Supporting; Writing – original draft: Supporting; Writing – review & editing: Supporting).

Conflicts of interest
The authors disclose no conflicts.

Funding
Dr Goldberg receives funding from the National Institutes of Health grant R01 DK120561.

Supplementary Table 1. List of International Classification of Diseases, 10 Revision Codes Included to Identify Patients With Liver Disease–related Mortality

Code	Code Name
C22.0	Liver cell carcinoma—malignant neoplasms
K70.0	Alcoholic fatty liver
K70.1	Alcoholic hepatitis
K70.2	Alcoholic fibrosis and sclerosis of liver
K70.3	Alcoholic cirrhosis of liver
K70.4	Alcoholic hepatic failure
K70.9	Alcoholic liver disease, unspecified
K71.7	Toxic liver disease with fibrosis and cirrhosis of liver
K73.0	Chronic persistent hepatitis, not elsewhere specified
K73.1	Chronic lobular hepatitis, not elsewhere classified
K73.2	Chronic active hepatitis, not elsewhere classified
K73.8	Other chronic hepatitis, not elsewhere classified
K73.9	Chronic hepatitis, unspecified
K74.0	Hepatic fibrosis
K74.1	Hepatic sclerosis
K74.2	Hepatic fibrosis with hepatic sclerosis
K74.3	Primary biliary cirrhosis
K74.4	Secondary biliary cirrhosis
K74.5	Biliary cirrhosis, unspecified
K74.6	Other and unspecified cirrhosis of liver
K76.6	Portal hypertension
K76.7	Hepatorenal syndrome

Supplementary Table 2. β Coefficients for All Covariates in Linear Regression Models Evaluating Factors Associated With County-level Age-adjusted Liver Disease–related Mortality Rates

Variable	β Coefficient	*P*	Unadjusted R^2
County-level racial/ethnic composition			
% White Hispanic	0.25 (0.21, 0.39)	<.001	0.08
% Black Hispanic	–1.05 (–1.99, –0.10)	.03	0.002
% Black non-Hispanic	–0.07 (–0.11, –0.04)	<.001	0.008
% Asian	–0.35 (–0.48, –0.22)	<.001	0.01
% Native American	1.07 (1.01, 1.12)	<.001	0.40
% Adults living below poverty level	0.83 (0.73, 0.93)	<.001	0.11
% Uninsured	0.76 (0.68, 0.83)	<.001	0.17
Miles to closest liver transplant center[a]	0.31 (0.27, 0.36)	<.001	0.08
Rural or urban status			0.05
Large metropolitan	Reference		
Small/medium metropolitan	3.63 (2.30, 4.98)	<.001	
Rural	6.39 (5.17, 7.62)	<.001	
Number of board-certified gastroenterologists	–0.04 (–0.06, –0.02)	<.001	0.008
% With diabetes	1.77 (1.56, 2.01)	<.001	0.09
% With obesity	0.52 (0.41, 0.63)	<.001	0.04
% With heavy alcohol use	0.20 (–0.009, 0.40)	.06	0.002
Listings per 100 deaths	–0.11 (–0.13, –0.10)	<.001	0.09

[a]Per 10-mile increments.