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Original Research Article

Mortality associated with chronic hepatitis C and liver cirrhosis: a retrospective study

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ABSTRACT

Background: Hepatitis C virus (HCV) infection is a leading cause of mortality; however, its relation with liver cirrhosis remains underexplored. Identifying high-risk populations and developing targeted public health initiatives requires an understanding of this association.
Methods: A retrospective observational study was conducted using the CDC MCD data to assess mortality trends among United States individuals aged 25 years and older between 1999 and 2020. Stratified by age, sex, race, geographical location, and place of death, the study analysed deaths with hepatitis C (ICD-10 code: B18.2) as the primary cause and liver cirrhosis (ICD-10 code: K74) as a contributing factor. Age-adjusted mortality rates (AAMRs) and annual percentage changes (APC) were calculated.
Results: The study period recorded 49,707 deaths. The AAMR declined from 1999 to 2003 (-16.44% APC), followed by an increase from 2003 to 2006 (+163.28%), and significantly decreased from 2006 to 2020 (-5.10%). Mortality was highest among males (64%), white individuals (81.7%), and metropolitan residents (84.9%). Temporal trend analysis revealed a steady decline in overall mortality rates in recent years, with significant variations across demographic and geographic groups.
Conclusions: The mortality trends in hepatitis C with liver cirrhosis have shifted from 1999 to 2020, with notable racial, regional, and gender disparities. This emphasizes the need for targeted prevention interventions and enhanced healthcare access.

Keywords: Hepatitis C, Liver cirrhosis, Age-adjusted mortality rate, Retrospective study, CDC MCD

INTRODUCTION

Chronic hepatitis C virus (HCV) infection remains a critical public health concern, contributing significantly to liver-related morbidity and mortality worldwide. In the United States, approximately 2.4 million individuals are living with HCV as of 2020, according to the centres for disease control and prevention (CDC).[1] Despite advances in antiviral therapy; HCV continues to be a leading cause of liver disease-related deaths. Disparities in HCV-related mortality are well documented, with elevated death rates observed among older adults, males, and racial minorities

particularly Black or African American populations due to barriers in healthcare access and delayed diagnosis.[2,3] Geographic disparities also persist, with higher mortality reported in rural and underserved areas.[4]

Liver cirrhosis, a condition characterized by progressive hepatic fibrosis and architectural disruption of the liver, is a common and severe consequence of chronic HCV infection. Cirrhosis significantly increases the risk of hepatic decompensation, liver failure, and hepatocellular carcinoma.[5] As a contributing cause of death, cirrhosis often coexists with HCV and compounds the risk of mortality. The burden of cirrhosis-related deaths is disproportionately higher among males, older adults, and individuals of lower socioeconomic status, reflecting systemic disparities in disease detection and treatment.[6] The pathophysiological relationship between HCV and liver cirrhosis is well established: persistent HCV infection drives chronic hepatic inflammation, activates stellate cells, and promotes fibrogenesis, culminating in cirrhosis and end-stage liver disease.[7] Studies have shown that coexisting cirrhosis in HCV-infected patients substantially worsens clinical outcomes and elevates the risk of mortality.[5-7] However, most mortality studies have focused on HCV as the primary cause of death, neglecting the impact of cirrhosis as a secondary contributor. While prior research has explored HCV mortality trends, few studies have examined how cirrhosis modifies these patterns, particularly in stratified demographic groups. The CDC multiple causes of death (MCD) database offer a unique opportunity to assess the joint impact of HCV and cirrhosis on mortality by including both underlying and contributing causes of death. This study aims to fill this gap by evaluating long-term mortality trends and demographic disparities in HCV-related deaths where liver cirrhosis was a contributing factor.

METHODS

This was a population-based study using the centres for CDC wide-ranging online data for epidemiologic research (CDC WONDER) MCD database.[8] This is a virtual, publicly available mortality data, which includes de-identified death certificate information for all deaths recorded in the United States, was used for the purpose of this study, and as the dataset comprises of publicly available, de-identified information, the study was classified as non-human participant research, thus exempt from institutional review board (IRB) approval.[9-12] Data extraction and analysis were performed virtually over a two-week period from April 28, 2025 to May 5, 2025. As this was a national database-based study using virtual publicly available data, it was not associated with any single hospital, healthcare facility, or institution. Mortality data was obtained from the CDC WONDER MCD database for the years 1999-2020. The age group considered for the study is 25 years or older, as HCV-related mortality is rare in younger populations. Hepatitis C (ICD-10: B18.2) was selected as the underlying cause of death, while liver cirrhosis (ICD-10: K74) was taken as the multiple cause of death to evaluate the co-occurrence of these conditions and records not meeting these inclusion criteria were excluded. Demographic variables such as gender (male and female) and race/ethnicity (American Indian or Alaska Native, Asian or Pacific Islander, Black or African American, White) were included to assess differences in mortality outcomes. Geographic variables included urbanization based on the 2013 classification, classifying metropolitan cities into large central metro, large fringe metro, medium metro, and small metro, and non-metropolitan cities into micropolitan and non-core rural areas. Place of death was categorized as medical facility, home, hospice, or nursing facility. Mortality rates were standardized according to age-adjusted rates per 1,000,000 populations by making adjustments based on the United States. Standard Population from the year 2000 to allow for accurate comparisons over the years. To summarize the demographic and geographic variables, descriptive statistics were used. Age-adjusted mortality rates were calculated for each subgroup using the CDC WONDER MCD database. To assess temporal trends, joinPoint regression analysis (JoinPoint Software Version 5.3.0.0, November 2024) was used to determine annual percentage changes (APC) in hepatitis C-related mortality with liver cirrhosis as a contributing cause. Trends were assessed over the 1999-2020 study period to identify statistically significant changes in mortality dynamics across different demographic and geographic groups.

RESULTS

Between 1999 and 2020, the CDC multiple causes of death (MCD) database documented a total of 49,707 deaths in the United States among individuals aged 25 years and older. The analysis included deaths in which hepatitis C (ICD-10:B18.2) was identified as the underlying cause of death and liver cirrhosis (ICD-10: K74) appeared as a contributing cause (49,707 deaths in total). Based on these data, the crude mortality rate for hepatitis C with liver cirrhosis as a contributing condition was 11.1 per 1,000,000 populations. Deaths that did not meet these criteria were excluded from the study.

Demographic characteristics

Of all deaths assessed, 17,904 (36%) occurred among females and 31,803 (64%) among males. Mortality rates were higher among males than females, suggesting a demographic disparity in risk. In terms of racial distribution, White individuals accounted for the majority of deaths, 40,061 (81.7%), followed by Black or African American individuals at 7,106 (14.3%). Asian or Pacific Islander individuals represented 1,298 (2.6%) deaths, while American Indian or Alaska Native individuals accounted for 689 (1.4%). The largest mortality burden was observed among White individuals, underscoring racial disparities in mortality associated with hepatitis C and liver cirrhosis.

Geographic characteristics

Most deaths occurred in metropolitan areas, 42,194 (84.9%), whereas 7,513 (15.1%) were reported in nonmetropolitan regions. With regard to location of death, medical facilities accounted for the largest proportion, 26,855 (54%). This was followed by deaths occurring at home, 11,659 (23.5%), in nursing homes or long-term care facilities, 5,098 (10.3%), and in hospice facilities, 3,930 (7.9%).

The overall demographic and geographic characteristics were represented in Table 1.

Table 1: Demographic and geographic characteristics of the study.

Demographic variable	number of deaths (N)	Percentage (%)
Gender		
Male	31803	64.00
Female	17904	36.00
Race		
American Indian or Alaska native	689	1.40
Asian or Pacific islander	1298	2.60
Black or African American	7106	14.30
White	40614	81.70
Urbanization		
Metropolitan area	42194	84.90
Large central metro	17252	34.70
Large fringe metro	9334	18.80
Medium metro	11038	22.20
Small metro	4570	9.20
Non- metropolitan area	7513	15.10
Micropolitan	4428	8.90
Non-core	3085	6.20
Place of death		
Medical facility	26855	54.00
Decedent's home	11659	23.50
Hospice facility	3930	7.90
Nursing home/long term care	5098	10.30
Other	2165	4.40

Temporal trends

From 1999 through 2003, the age-adjusted mortality rate (AAMR) for hepatitis C with liver cirrhosis as a contributing cause showed a significant decline, with an annual percentage change (APC) of –16.44% ($P<0.05$). However, between 2003 and 2006, the AAMR rose sharply, with an APC of +163.28% ($P<0.05$). A subsequent decrease was noted from 2006 through 2020, with an APC of –5.10% ($P<0.05$). These results highlight a shift in mortality patterns over the past two decades, with the most recent period showing a decline in AAMR as shown in Figure 1.

Gender-specific trends

Among females, the AAMR initially decreased between 1999 and 2003 (APC: –16.29%). This was followed by a significant rise from 2003 to 2006 (APC: +147.92%). After 2006, a consistent decline was observed through 2020 (APC: –4.46%), suggesting a reduction in mortality risk in more recent years. For males, a similar pattern was evident: an initial decline from 1999 to 2003 (APC:–15.01%), a sharp increase between 2003 and 2006 (APC: +166.38%), and then a marked decline from 2006 to 2020 (APC: –5.33%) as depicted in Figure 2.

Racial disparities

White individuals displayed the highest AAMR. Their mortality trends showed an initial decrease between 1999 and 2003 (APC: –15.50%), followed by a sharp rise from 2003 to 2006 (APC: +160.44%), and then a steady decline from 2006 to 2020 (APC: –4.91%).

Trends for the Black or African American, American Indian/Alaska Native, and the Asian or Pacific Islander populations were not presented due to the data suppression for counts fewer than 10, which limited the reliability of trend estimates as shown in Figure 3.

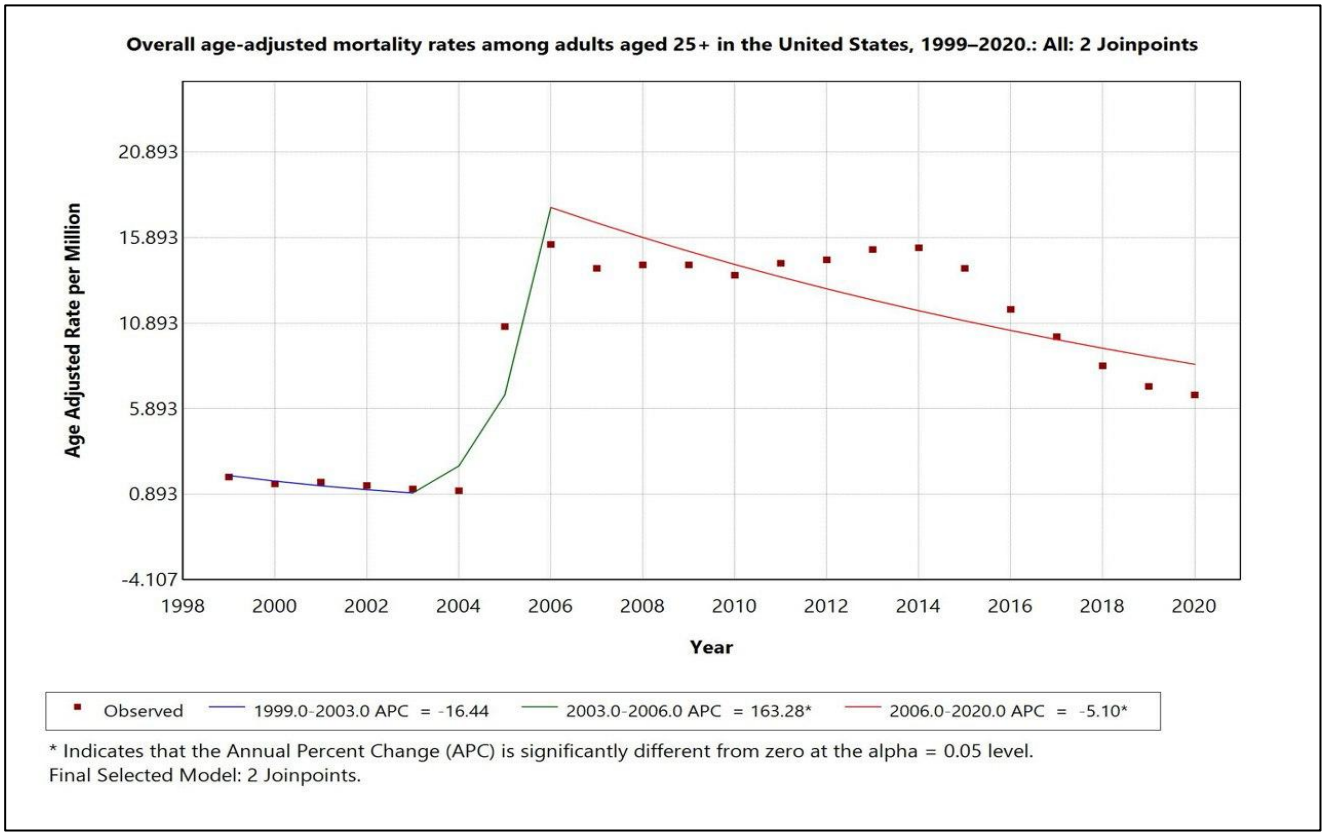

Figure 1: Overall age-adjusted mortality rates among adults aged 25+ in the United States, 1999-2020.

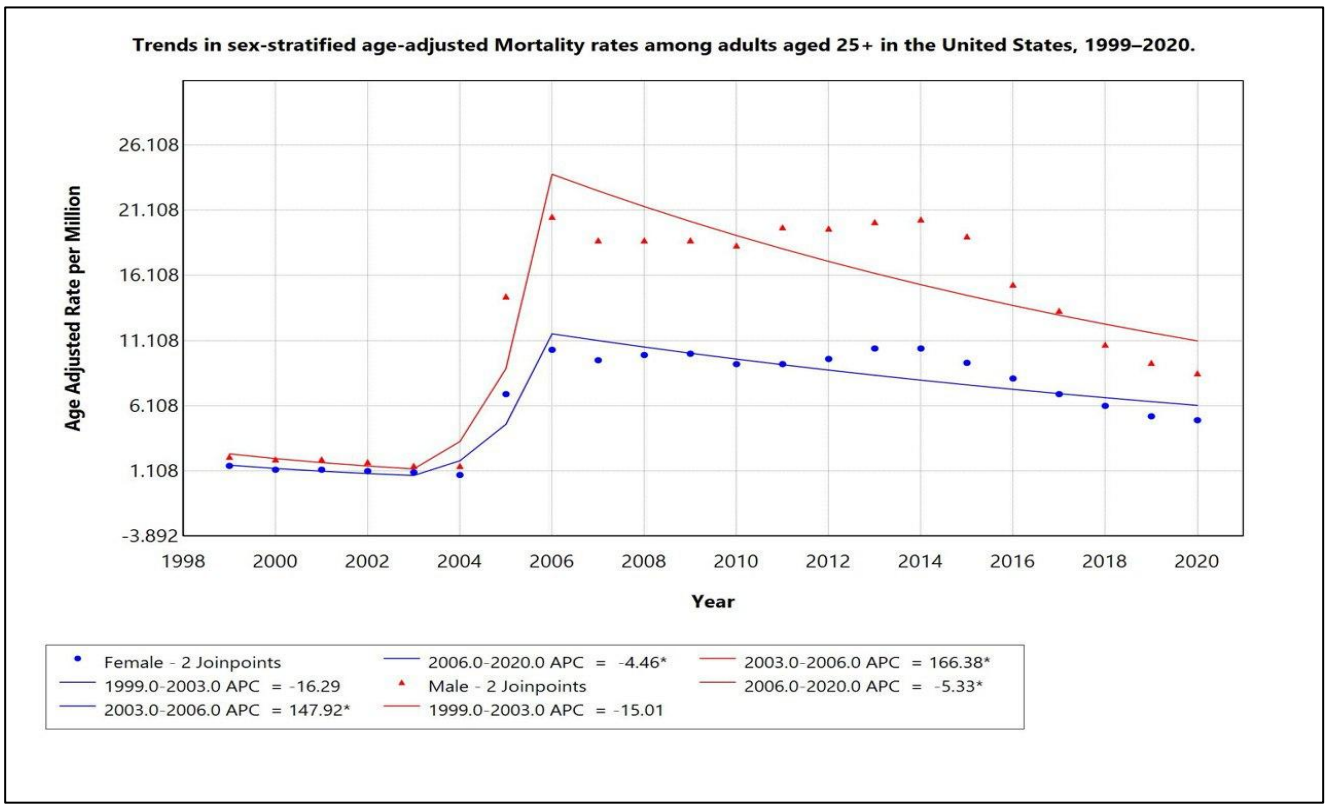

Figure 2: Trends in sex-stratified age-adjusted mortality rates among adults aged 25+ in the United States, 1999-2020.

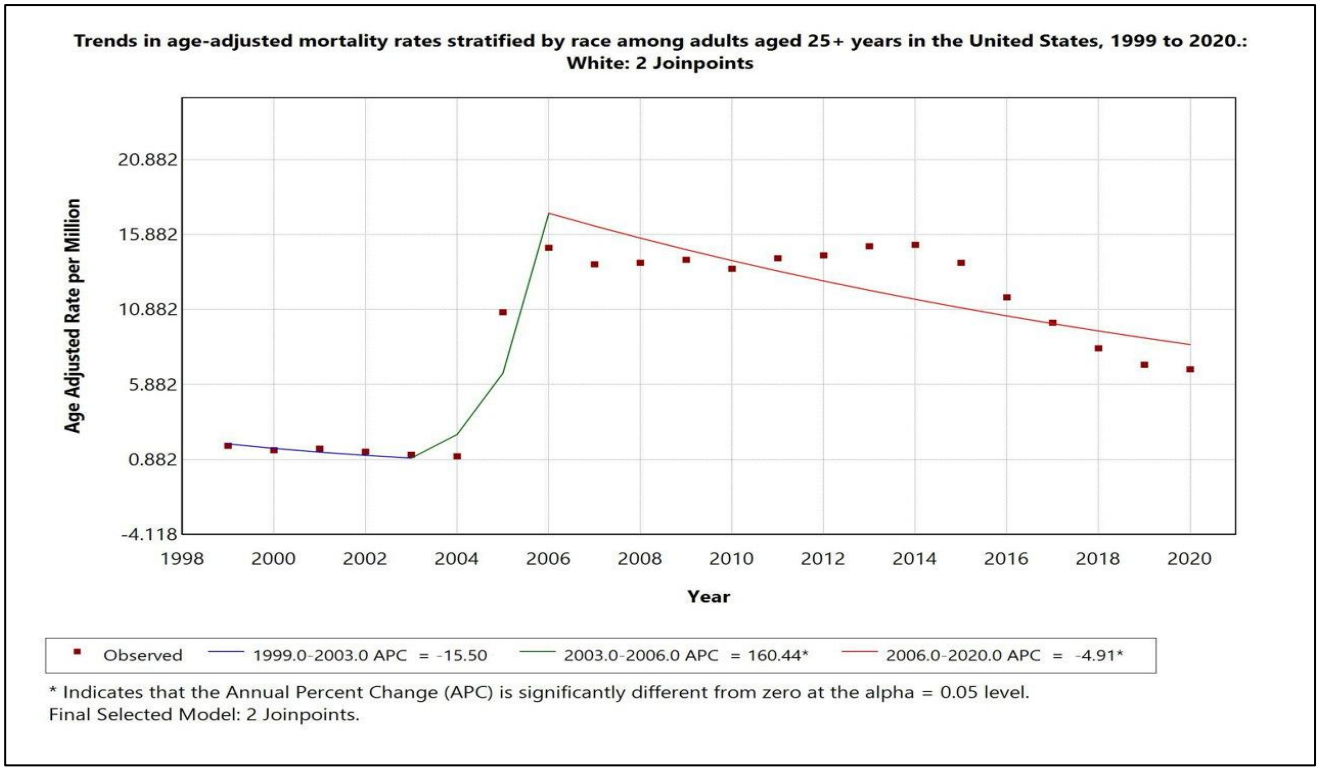

Figure 3: Trends in age-adjusted mortality rates stratified by race among adults aged 25+ years in the United States, 1999- 2020.

DISCUSSION

The MCD database from CDC WONDER was taken for this retrospective original study. This study examined the trend of mortality due to hepatitis C (B18.2) and liver cirrhosis (K74) as contributing causes in the adult population aged 25 and over within the United States during the period from 1999 to 2020. 497,070 deaths were registered, with a crude mortality rate of 11.1 per million over the 21 years. Changing trends in AAMR for hepatitis C with liver cirrhosis showed an initial decrease from 1999 to 2003 (APC: -16.44%), followed by a sharp increase from 2003 to 2006 (APC: +163.28%). Thereafter, the decline set in again from 2006 to 2020 (APC: -5.10%). Mortality rates remained the highest among the White population. Males stood at 64% of the deaths; Whites constituted 81.70% of these deaths, and 84.90% were from metropolitan areas.

The pathophysiology linking HCV infection and liver cirrhosis is the common pathway of chronic liver injury. A long-term course of HCV infection leads to hepatic inflammation, fibrosis, and ultimately cirrhosis, which greatly elevates the risk of decompensation of the liver and hepatocellular carcinoma.[13,14] In fact, it has been consistently described that HCV is among the primary aetiologies of liver-related mortality worldwide; especially when aggravating factors such as cirrhosis are involved.[15] The progression from HCV to cirrhosis involves persistent hepatic injury, activation of hepatic stellate cells, and fibrogenesis, leading to architectural distortion and liver dysfunction.[16] These processes collectively contribute to elevated mortality rates, particularly in patients who remain undiagnosed or untreated.

The overall AAMR for hepatitis C with liver cirrhosis in this study aligns with previous national estimates. The AAMR was found to be 11.1 per million, with Joinpoint regression indicating a significantly declining APC in recent years likely attributable to improved antiviral treatments, such as the advent of direct-acting antivirals (DAAs) post-2014.[17,18] Similar findings were reported by Ly et al, who observed a decrease in HCV-related mortality following the introduction of DAAs.[19] However, our study provides novel insights by stratifying mortality by geographic area and urbanisation status, which has not been adequately characterised in earlier research.

The gender-based analysis revealed a striking disparity, with males accounting for 64% of deaths. This finding is consistent with prior literature indicating that males have a higher risk of HCV acquisition and a more rapid progression to cirrhosis and hepatocellular carcinoma.[20,21] Possible explanations include biological susceptibility, behavioural risk factors (such as higher rates of intravenous drug use), and reduced healthcare-seeking behaviour among men.[19] Racial disparities were also evident: while whites represented the highest absolute number of deaths, Black or African American individuals exhibited a disproportionately higher burden relative to population size, echoing prior research that attributes such disparities to socioeconomic factors, barriers to healthcare

access, and delayed treatment initiation.[3] However in a study conducted by Kolluri et al, found that the highest mortality rate was observed in females, the white population, and metropolitan areas. Temporal trends in NAFLD with liver cirrhosis showed an increase, with disparities noted across demographic and geographic factors.[22] Geographic analysis indicated that metropolitan areas particularly large central metros reported the highest number of deaths. However, when adjusted for population, non-metropolitan areas may exhibit higher per-capita mortality due to limited healthcare infrastructure, fewer specialists, and challenges in accessing advanced antiviral therapies.[23] These findings suggest that regional public health initiatives should prioritise rural and underserved populations to enhance screening, linkage to care, and treatment uptake.

Temporal trend analysis revealed a consistent decline in overall mortality rates over the past few years. However, significant disparities persist in mortality outcomes based on gender and race. This decline is attributed to increased screening efforts and the introduction of DAAs. Nevertheless, not all populations have benefited equally from these advancements. Studies indicate that certain racial and rural populations continue to face substantial barriers to accessing HCV testing and treatment. Consequently, their mortality outcomes have not experienced the same level of improvement as other populations. The implications of these findings for public health are substantial. There is an urgent need to address treatment disparities, enhance HCV screening programs, and improve access to antiviral therapies, particularly in rural and minority populations. Future research should explore policy-level interventions, such as Medicaid expansion or community-based treatment models, to effectively reduce these disparities. Additionally, efforts to raise awareness and reduce stigma surrounding HCV testing and treatment may contribute to improved outcomes for vulnerable populations.

Limitations

This study is subject to certain limitations: inaccuracies in coding the death certificate data and factors related to comorbidities and treatment history were not considered. Changes in diagnostic and reporting practices may have influenced the trend. Being a retrospective observational study, cannot be stated with certainty that it establishes causation. It was also not considered that factors such as socioeconomic status, availability of health services, and lifestyle preferences were missing from the MCD database, which might, in fact, be the confounding factors for the observations given above.

CONCLUSION

This research into the mortality trends from 1999 through 2020 in the United States. For those 25 years and older-focused on hepatitis C (B18.2) and liver cirrhosis (K74) as major causes. A total of 49,707 deaths were recorded, with the highest age-adjusted mortality rates for any cause prevalent primarily among males, White populations, and metropolitan residents. Though overall mortality tended to decrease with time, there are certain trends that have persisted across gender, racial, and geographic groups. These findings spotlight on-going disparities, especially between males and non-Hispanic Whites as the deprived. Geographic variation suggests healthcare access and regional risk factors as an influence. Clinically and from a public health standpoint, this further solidifies the need for targeted interventions and prioritization of resources in high-risk deprived populations. Future research should commence toward uncovering major causes of these disparities; subsequent to that, preventive strategies and policy measures focusing on reduction in Hepatitis C-liver disease mortality should be evaluated for effectiveness.

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