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■ RESEARCH ARTICLE

Trends in Chronic Liver Disease Mortality Rates during the COVID-19 Pandemic

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ABSTRACT: This study was performed to analyze trends in chronic liver disease and influenza during the COVID-19 pandemic. The CDC VSRR database and the CDC NHSS Pressroom Database were used to analyze chronic liver disease mortality rates from 2014 to 2020. Secondary, state level data was analyzed to look for potential correlation between mortality rates and "strictness" of COVID-19 restrictions. From 2014-2020, there was a slight increase in national yearly deaths with a large increase seen between 2019 and 2020. When analyzing 2019 to 2020 quarterly data, rates appear to increase rapidly after 2019 Q4. In the state-wide analysis, it was found that states with less restrictive COVID-19 guidelines had higher mortalities and mortality rates of chronic liver disease; Iowa saw the highest increase from 2019 Q4 to 2020 Q4 in chronic liver disease/cirrhosis mortality rates at 38.6%, followed by Nevada at 23.1%, and by Virginia at 22.1%. During the COVID-19 pandemic, national chronic liver disease mortality rates significantly increased. There seems to be an association between mortality rates and the "strictness" of COVID-19 restrictions at a state level.

KEYWORDS: Translational Medical Sciences; Disease Prevention; COVID-19; Pandemic; chronic liver disease.

■ Introduction

Chronic liver disease is the 9th leading cause of death in the US, and the 11th leading cause of death in the world.[1,2] It is in the top 20 causes of disability-adjusted years of life lost, and accounts for roughly 2% of the worldwide burden. It's yearly economic burden in the US is approximately 2.5 billion dollars.[3] The healthcare cost was $17,277 for non-cirrhosis patients, $22,572 for compensated cirrhosis patients, and $59,995 for patients in the final stages of liver disease, with an estimated national healthcare cost of 32 billion dollars annually.[4] Liver cirrhosis is the final stage in liver disease, which is the progressive deterioration of liver functions, caused by scar tissue replacing healthy tissue in the liver.[5,6] Although mortality rates vary, those in the moderate stages of liver disease have a 60% chance of survival over a two year period.[7] Those with compensated liver disease have a median life expectancy of 12 years, while those with decompensated liver failure have a median life expectancy of 2 years.[8] Most people afflicted by this condition in the US are ages 45-54.[9] Although there is no definitive cure for chronic liver disease, common treatments include: general lifestyle changes (reduced alcohol consumption, losing weight, changes in diet), certain medications, and in extreme cases, liver transplants.

On January 21st, 2020, the first case of COVID-19 in the contiguous 48 states was confirmed.[10] As of October 2021, there have been 44.9 million cases and 724,000 deaths due to COVID-19 in the United States.[11] The estimated projected total economic burden of COVID-19 is $16 trillion.[12] This is including but not limited to: economic losses due to cumulative and premature deaths, long-term complications, and mental health symptoms. It caused states to impose lockdowns, close schools, and enforce curfews, all of which negatively affected the population. During the ongoing COVID-19 pandemic, influenza rates have dropped significantly.[13] This study has explored the trends observed in chronic liver disease mortalities compared to influenza during the COVID-19 pandemic. It analyzed the effect of distinct levels of statewide COVID-19 restrictions on that state's liver disease mortality levels. By doing this, provided new insight into the direct correlation between chronic liver disease and COVID-19.

■ Methods

Data Source:

Data were acquired from the CDC VSRR Mortality Database, the CDC NCHS Pressroom Database, and the United States Census Bureau.[14-17] The CDC VSRR Mortality Database collects quarterly mortality data by age, state, sex, and cause of death from 2019-2020. The Census Bureau has been collecting population data since 1903 and was used to collect yearly populations from 2014-2020. Quarterly populations were not available, so quarterly mortality rates were derived using yearly populations. The data was divided into yearly deaths and mortality rates from 2014-2020, as well as quarterly mortality rates from 2019-2020 due to the lack of available quarterly data (for both deaths and mortality rates) from 2014-2018. Because this study used publicly available de-identified data, the study was determined to be exempt from Institutional Review Board review.

Inclusion Criteria:

Chronic liver disease/cirrhosis (abbreviated as LD) deaths as defined in the CDC VSRR Mortality Database were included. Influenza/pneumonia (referred to as influenza going forward) deaths were also extracted as a control. For each disease, yearly death counts and crude mortality rates are reported with quarterly data presented for only 2019-2020. Deaths were examined at a national level with secondary analysis including three specific states selected based on the

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severity of that state's COVID-19 restrictions. The included states were Iowa, Nevada, and Virginia, listed in order of increasing COVID-19 restrictions.[18]

Statistical Analysis:

The crude rates per 100,000 people were calculated using the CDC VSRR mortality data, the CDC NHSS mortality data, and the US Census Bureau population data. Linear regression analyses with Pearson correlation were performed to study mortality trends from 2014-2020. For the quarterly percent difference between 2019 Q4 and 2020 Q4, the CDC VSRR database has already calculated the statistical significance so additional analysis of the yearly Q4 difference from 2019-2020 was not performed, and the provided results were used.[15]

Results and Discussion

Both death counts and mortality rates as a result of COVID-19 were analyzed nationally and in three individual states (Iowa, Nevada, Virginia). This data is presented both yearly (from 2014-2020) and quarterly (from 2019 Q1-2020 Q4). According to Becker's Hospital Review, Iowa had the least restrictions, Nevada was ranked 29th least strict, and Virginia was the strictest of the states in terms of COVID-19 restrictions and policies.[18]

Chronic Liver Disease/Cirrhosis Mortality Rate Trends:

From 2014-2020, there was a slight increase in national yearly deaths with a large increase seen between 2019 and 2020 (Figure 1).

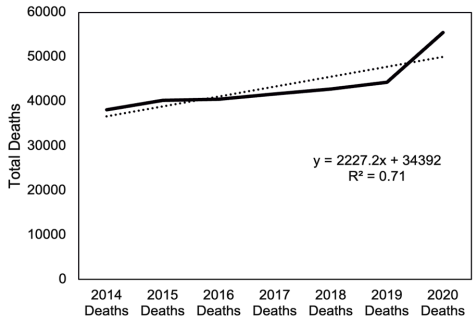

Figure 1: 2014-2020 yearly liver disease/cirrhosis crude deaths, β = 2227.2 deaths per year; R^2 = 0.71.

A similar trend is seen for mortality rates for 2014-2020, with a steady yearly increase, followed by a large spike in mortality rates in 2019-2020 (Figure 2).

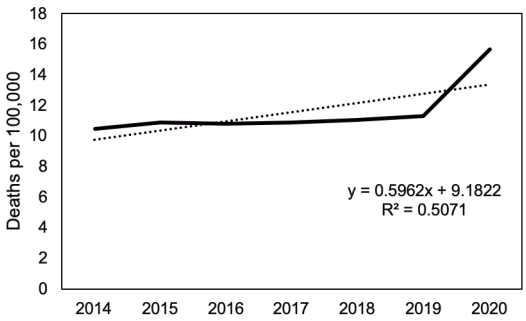

Figure 2: 2014-2020 yearly chronic liver disease/cirrhosis crude mortality rates, β = 0.5962 deaths per 100,000 per year.

When analyzing 2019 to 2020 quarterly data, rates appear to increase rapidly after 2019 Q4, corresponding with the start of COVID-19 (Figure 3).

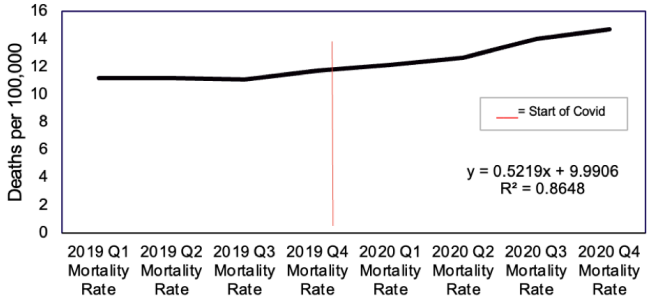

Figure 3: 2019-2020 quarterly chronic liver disease/cirrhosis crude mortality rates.

There is a statistically significant difference between 2019 Q4 and 2020 Q4 according to the CDC VSRR database, with a national percent increase of 22.0% (Table 1).[15]

Table 1: 2019 Q^4 to 2020 Q^4 chronic liver disease/cirrhosis crude mortality rate change by state.

	2019 Q4 Mortality Rate (Deaths per 100,000)	2020 Q4 Mortality Rate (Deaths per 100,000)	Percent Change from 2019 Q4 to 2020 Q4
Iowa	11.4	15.8	38.6*
Nevada	16.0	19.7	23.1*
Virginia	11.6	14.9	22.1*
US	14.1	17.2	22.0*

*Denotes statistical difference between 2019 Q4 and 2020 Q4 ($P < 0.05$) according to the CDC VSRR database.

The data from the three states showed that the total percent increase was inversely proportional to how strict that state was; Iowa saw the highest increase in chronic liver disease/cirrhosis mortality rates at 38.6%, followed by Nevada at 23.1%, and by Virginia at 22.1% (Table 1). This was although stricter states like Nevada and Virginia both maintained overall mortality rates that were higher than the least strict state - Iowa. The interquartile fluctuations in the data were represented by the quarterly mortality rates of each state (Figure 4).

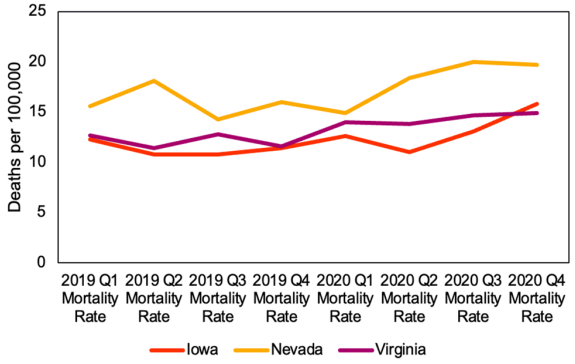

Figure 4: 2019-2020 quarterly chronic liver disease/cirrhosis crude mortality rates by state.

Influenza/Pneumonia Mortality Rate Trends:

During 2014-2020, there was an average annual decline in the national mortality rate of influenza/pneumonia. (Figure 5).

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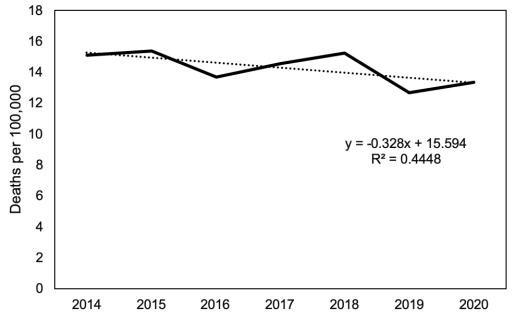

Figure 5: 2014-2020 yearly influenza/pneumonia crude mortality rates, β= -0.328 deaths per 100,000 per year.

Upon closer examination, the national mortality rate reached its minimum in 2019 Q3 and 2020 Q3, separated by a large peak in 2020 Q1, as well as a rapid increase and decrease in 2019 Q4 and 2020 Q2 respectively (Figure 6).

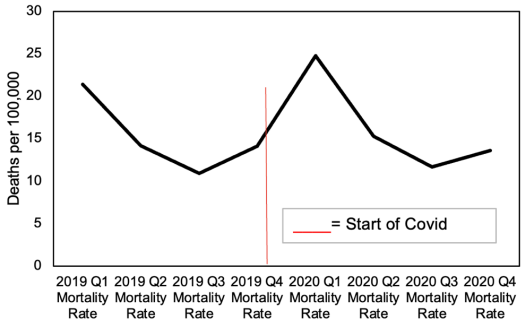

Figure 6: 2019-2020 quarterly influenza/pneumonia crude mortality rate.

This pattern of rapid increase and decrease was also present in the state data, as data from all three states (Iowa, Nevada, Virginia) showed a sharp incline in 2019 Q4, followed by a peak in 2020 Q1, and a sharp decline in 2020 Q2 (Figure 7).

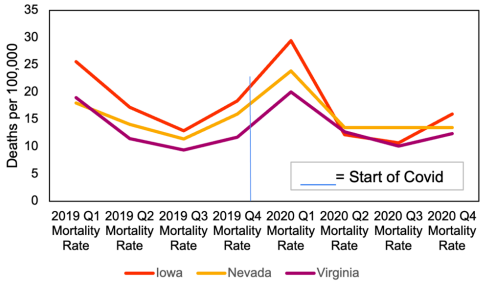

Figure 7: 2019-2020 quarterly influenza/pneumonia crude mortality rate by state.

The national mortality rate was 14.1 in 2019 Q4, and 13.6 in 2020 Q4, resulting in a percent decrease of 3.7%, a change that has statistical significance, as stated by the CDC VSRR database (Table 2).[15]

Table 2: 2019 Q4 to 2020 Q4 pneumonia/Influenza Crude Mortality Rate Change by State.

	2019 Q4 Mortality Rate (Deaths per 100,000)	2020 Q4 Mortality Rate (Deaths per 100,000)	Percent Change from 2019 Q4 to 2020 Q4
Iowa	18.4	16.0	13.0*
Nevada	16.0	13.5	15.6*
Virginia	11.7	12.4	6.0
US	14.1	13.6	3.7*

*Denotes statistically difference between 2019 Q4 and 2020 Q4 (P < 0.05) according to CDC VSRR database.

Iowa and Nevada had percent decreases of 13.0% and 15.6% respectively (both of which were statistically significant as stated by the CDC VSRR database), while Virginia had a percent decrease of only 6.0% (not statistically significant).[15]

In this comparative study of national and statewide chronic liver disease/cirrhosis and pneumonia/influenza trends over a 7-year period, it was found that LD mortalities followed a slightly upward sloping trend, followed by a sudden rise in 2019-2020. Influenza mortality numbers repeated a triannual pattern in which they rose to a peak, and then declined, which continued even after the start of COVID-19.

For example, LD increased by 22%, and influenza decreased by only 3.7% from 2019 Q4 to 2020 Q4. It has widely been discussed that influenza numbers were at an all-time low during the pandemic. Studies hypothesize that this was caused by precautions taken to slow the spread of COVID-19, such as practicing social distancing and wearing masks.[19] While literature points to reasons such as these for the decrease in influenza, there may be other reasons contributing to the significant increase in LD mortality rates. The abrupt increase in LD seems to line up with when COVID-19 first started (2019 Q4), indicating that there may be some association there. Three potential explanations for the increase in LD deaths arise: 1) direct impact of COVID-19 virus on the liver, 2) increased alcohol consumption during pandemic, 3) restricted availability of healthcare facilities during the pandemic and likely all 3 of these contributed to the 22.0% increase in LD deaths between 2019 Q4 and 2020 Q4.

Patients that have been hospitalized due to COVID-19 have been tested, and often show an increased level of liver enzymes such as alanine aminotransferase (ALT).[20] The buildup of enzymes like these temporarily damages the liver for the entire duration of the illness. For people unaffected by liver disease, this may not be a problem. But, for patients whose livers are already compromised due to a pre-existing condition such as chronic liver disease or cirrhosis, this may accelerate the progression of their illness. Following the infection of COVID-19, patients are at risk of increased rates of hepatic decompensation, acute liver failure, and death due to respiratory failure.[21]

After the initial progression of COVID-19 in early 2020, worldwide lockdowns and restrictions were implemented, resulting in an extended period of extreme stress and disconnectedness from other people. Around 60.1% of people have said that their alcohol consumption increased during the pandemic, 45.7% of whom quoted increased stress, and 30.1% of whom quoted increased boredom.[22] Unhealthy eating habits and disorders have seen reemergence during the pandemic, another potential cause of increasing LD mortalities. A second potential explanation for the increase in LD deaths was the restricted availability of healthcare facilities for those with non-COVID-19 related ailments. A pulse survey conducted in February 2021 by the US Department of Health and Human Services (HSS) found that surges in COVID patients caused most hospitals to restrict the number of patients with non-COVID related illnesses they could treat.[23] A lack of available nearby medical facilities may have prevented some LD patients from receiving treatments that they normally would have received in the

absence of a pandemic like this one. In addition to this, those with LD might have chosen to skip regular checkups for their liver condition out of the fear of the coronavirus itself, since hospitals themselves were flooded with COVID-19 patients. Unfortunately, it is not possible to tease out which and how much each of these three factors affected/caused the increase in LD deaths seen.

A state level analysis of LD deaths was also conducted. Out of the three states (Iowa, Nevada, Virginia) analyzed, COVID-19 restrictions of each state appear to influence the number of LD mortalities. Data from the three states show that states with less strict COVID-19 restrictions had higher percent increases of LD mortality rates from 2019 Q4 to 2020 Q4 (Iowa-38.6%, Nevada - 23.1%, Virginia- 22.1%). Iowa had the least restrictions and had a significantly higher percent increase in LD mortality rates from 2019 Q4 to 2020 Q4.[15] Although Virginia was the strictest in terms of COVID restrictions, its percent increase was only significantly lower than Iowa, not Nevada. This difference in COVID-19 restrictions between Iowa and Virginia shows the efficacy (and inefficacy) of the guidelines in stopping the increase of LD mortalities. In late 2020, Iowa lifted all bar/restaurant curfews, as well as social gathering limitations, which explains the increase in the mortality rate of Iowa in 2020 Q3 and 2020 Q4.[24] Until March 1st of 2021, Virginia residents had a mandatory curfew from midnight to 5 AM, indoor and outdoor gathering limits of 10 people, as well as 30% capacity for both indoor and outdoor entertainment.[24] This change in restrictions offers an explanation for the gradual increase in the LD mortality rate throughout the entirety of 2020 Q2. These restrictions, as well as how late Virginia eased up on restrictions compared to Iowa, highlight a connection between the LD mortality rate of a state with the severity of its COVID-19 guidelines. Las Vegas is Nevada's largest tourist attraction, and with borders closed, and statewide lockdowns enforced, tourism rates decreased notably. Specifically, visitor volume decreased by 55% compared to 2019, so a decrease in LD deaths was to be expected, offering a potential explanation for why Nevada and Virginia have similar mortality rate percent increases from 2019 Q4 to 2020 Q4 despite differences in COVID restrictions.[25]

Despite the associations reported here, there were some limitations that must be acknowledged. This data was collected using national databases, and with some numbers being self-reported by states, there is a level of internal bias to be expected, to preserve the stature of the state. Here, it was assumed that the differences in mortality rates of the states of interest is directly associated with the strictness of that state's COVID-19 restrictions, however there may be some overlooked variable(s) that may also be responsible for this finding. Although states were selected based on their COVID-19 guidelines, other variations between the states may be responsible for these numbers.

Conclusion

During COVID-19 pandemic, national chronic liver disease mortality rates significantly increased. There seemed to be an association between mortality rates and the "strictness" of COVID-19 restrictions at a state level. As new variants emerge and the pandemic continues, patients with chronic liver disease should be closely monitored and states should better incorporate this high-risk patient population into public health decision making.

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