Most excess years of potential life loss among individuals with cirrhosis during the pandemic were not related to COVID-19

We read with interest the article by Dufour *et al*.[1] The authors were to be commended for their comprehensive review on the presentations, pathophysiology and prognosis of COVID-19 in patients with chronic liver disease. Notably, the authors included data from multicentre and nationwide cohort studies to suggest decompensated cirrhosis as an independent risk factor for severe COVID-19 and death.[1–6]

However, while excess death from COVID-19 among patients with cirrhosis is important, the non-COVID-19-related excess death is integral in considering the degree of care disruption and delayed presentation, especially for those before 65 years of age. Thus, using the CDC WONDER website of the US National Vital Statistic System, which includes over 99% of deaths annually, we evaluated the percentage of excess years of potential life loss (YPLL) among individuals with cirrhosis during the pandemic and how much of these excess YPLL were directly versus indirectly related to COVID-19. Details of method are included in the online supplemental file. In brief, we included decedents with cirrhosis listed as one of the causes of death in the death certificate. We estimated cirrhosis-related premature deaths by calculating the YPLL.[7 8] We then conducted forecast analysis to estimate the projected YPLL according to the pre-pandemic YPLL. Excess YPLL was defined by the difference between projected and observed YPLLs. Proportion of COVID-19 is calculated as YPLL secondary to COVID-19-related death among patients with cirrhosis divided by excess YPLL for cirrhosis.

In total, 466 356 cirrhosis-related deaths aged 25–64 years during 1 January 2012–31 December 2021 were identified. The total YPLL (per 100 000 persons) increased from 376.4 in 2019 to 454.0 in 2020 and 491.0 in 2021, with an annual percentage change (APC) of 15.4% (p<0.001) between 2019 and 2021 via joinpoint analysis (figure 1A). When compared with projected YPLL in the corresponding years, this translated to an excess YPLL of 20.7% in 2020 and 29.5% in 2021, respectively. Notably, COVID-19-related YPLL constituted only a minority of the excess YPLL (20.1% in 2020 and 22.8% in 2021) (table 1).

By sex, the increasing trend of YPLL was more pronounced in female as compared with male (APC, 2.4% vs 0.2%) before the pandemic (figure 1B,C). During the pandemic, the upward trend became steeper while becoming more similar between female and male (APC, 14.9% vs 15.7%). For both sexes, the observed YPLLs were significantly higher than the projected YPLLs, and the proportions of COVID-19-related YPLL were similar (table 1).

By aetiology, while the percentage differences between the observed and projected YPLLs were pronounced across all etiologies, it was most prominent with alcohol-associated liver disease (ALD, 29.1% in 2020 and 40.7% in 2021), with the APC for ALD being 22.2% (95% CI 7.9% to 38.3%; p=0.009) during the pandemic (vs 2.5%, 95% CI 0.8% to 4.2%,

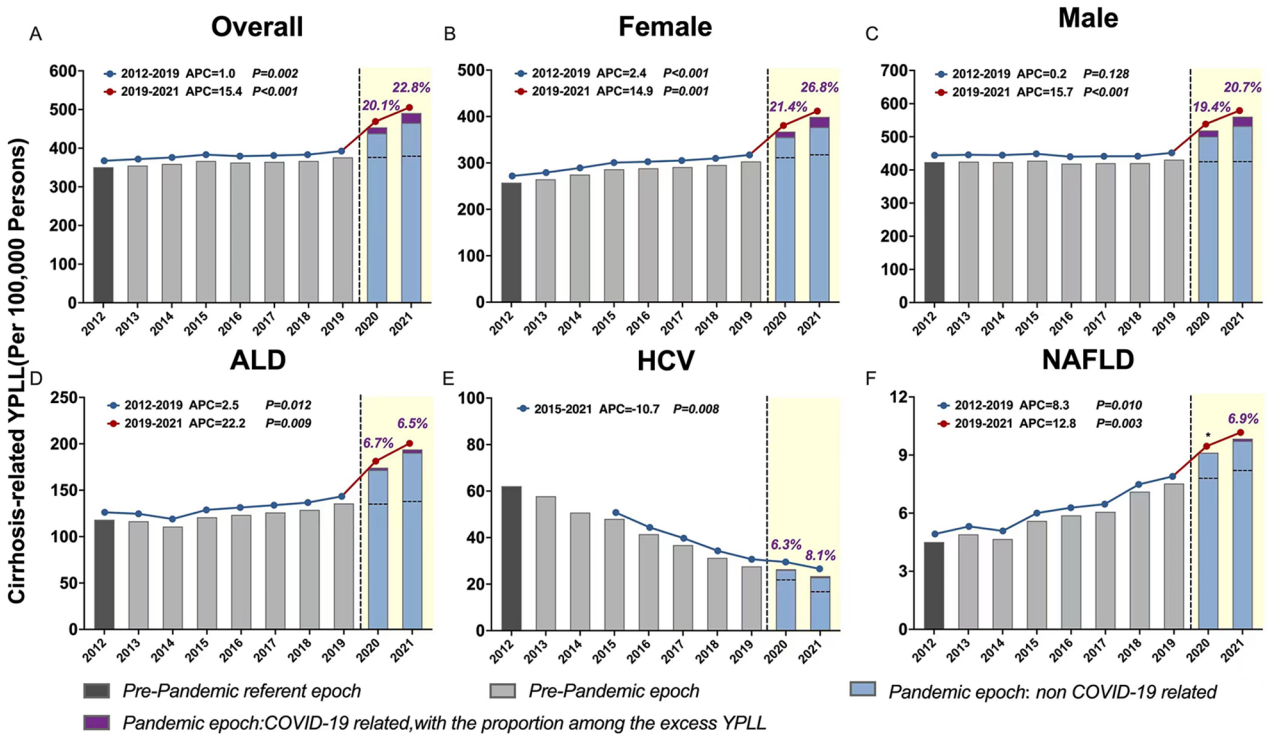

Figure 1 Years of potential life lost (YPLL) from premature deaths (<65 years of age) attributable to cirrhosis per 100 000 persons in the USA between 2012 and 2021 overall, by sex or by aetiology. Data shown for observed values versus predicted values (dashed line) for 2020 and 2021 based on data between 2012 and 2019 for each subgroup (except for HCV, of whom the predicted values were based on the 2015~2019 trend to align with the introduction of new direct acting antivirals in 2014). *Subgroups with less than 40 cases of COVID-19-related deaths (eg, NAFLD in 2020). Red line denotes that the change of YPLL during the pandemic was significant based on joinpoint analysis. Data on HBV infection-related mortality were not shown as the sample sizes of COVID-19 in both 2020 and 2021 were less than 40 cases. ALD, alcohol-associated liver disease; HCV, hepatitis C virus infection; NAFLD, non-alcoholic fatty liver disease.

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Table 1 Years of potential life lost (YPLL) from premature deaths (<65 years of age) attributable to cirrhosis per 100 000 persons in the USA between 2012 and 2021 overall, by sex or by aetiology

	YPLL per 100 000 persons									
	2012	2019	2020				2021			
	Observed	Observed	Observed	Predicted (95% CI)	Excess (%)	Proportion of COVID-19 (%)	Observed	Predicted (95% CI)	Excess (%)	Proportion of COVID-19 (%)
Overall	**350.8**	**376.4**	**454.0**	**376.3 (370.2 to 382.5)**	**20.7%**	**20.1%**	**491.0**	**379.3 (372.1 to 386.6)**	**29.5%**	**22.8%**
Sex										
Female	257.4	303.5	367.7	311.1 (303.9 to 318.3)	18.1%	21.4%	399.2	317.4 (308.9 to 325.8)	25.8%	26.8%
Male	423.4	431.2	519.2	424.7 (416.4 to 433.1)	22.2%	19.4%	560.6	424.9 (415.1 to 434.7)	31.9%	20.7%
Aetiology										
ALD	118.2	135.8	174.4	135.1 (127.3 to 142.8)	29.1%	6.7%	194.0	137.8 (128.7 to 147.0)	40.7%	6.5%
NAFLD	4.5	7.5	9.1	7.8 (7.2 to 8.4)	17.7%	–	9.9	8.2 (7.5 to 8.9)	20.3%	6.9%
HCV	62.1	27.6	26.4	21.8 (18.9 to 24.6)	21.1%	6.3%	23.5	16.7 (13.0 to 20.3)	40.7%	8.1%
HBV	5.5	3.4	3.4	2.8 (2.1 to 3.4)	23.3%	–	3.2	2.5 (1.7 to 3.2)	28.6%	–

Excess (%) is calculated as (Observed – Predicted)*100%/Predicted.
Predicted values for 2020 and 2021 were based on the 2012~2019 trend for each subgroup (except for HCV, of whom the predicted values were based on the 2015~2019 trend to align with the introduction of new direct acting antivirals in 2014).
Proportion of COVID-19 is calculated as YPLL secondary to COVID-19-related death among patients with cirrhosis divided by excess YPLL for cirrhosis in 2020 and 2021 (except for subgroups with less than 40 cases of COVID-19 related deaths (NAFLD in 2020 and HBV in both 2020 and 2021)).
ALD, alcohol-associated liver disease; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; NAFLD, non-alcoholic fatty liver disease; YPLL, years of potential life lost.

p=0.012, pre-pandemic) (figure 1D). The YPLLs for HCV and HBV infection were decreasing throughout the entire study time, but the decreasing trend became slower during the pandemic, resulting in considerable excess YPLLs for both of these subgroups (figure 1E). The percentages of excess YPLL for non-alcohol fatty liver disease were 17.7% in 2020 and 20.3% in 2021 (figure 1F). Importantly, COVID-19-related YPLL was less than 9% of the excess YPLL across all liver disease aetiologies (table 1).

YPLL for ALD has the most striking increase among all aetiologies. This is consistent with the report regarding elevated alcohol sales across the USA during the pandemic.[9] Increased stress, isolation-related boredom due to shelter-in-place orders, loss of familial and social support system, stigmatisation of disease and lack of access to mental health services were potential contributing factors.[10]

In conclusion, using nationwide data, we found a substantial increase in excess premature deaths that were related to cirrhosis during the pandemic in the USA, but less than 22.8% of cirrhosis-related excess YPLLs were associated with COVID-19 itself. This suggests that the majority of the excess premature deaths were resulted from the indirect impact of the pandemic, such as disruption of healthcare delivery, financial distress, social isolation and fear of contracting COVID-19. Therefore, 'returning to normal' of healthcare access and reception should be the goal for all stakeholders.

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