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MINIREVIEWS

Mortality from chronic liver disease: Recent trends and impact of the COVID-19 pandemic

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Abstract

Prepandemic time trends in mortality from chronic liver disease (CLD) differed according to specific cause of death (decreasing for liver cirrhosis, stable or increasing for liver cancer), etiology (increasing for nonalcoholic fatty liver disease, generally decreasing for other etiologies), and world region (decreasing in areas with the highest burden of hepatitis B virus, increasing in Eastern Europe and other countries). The coronavirus disease 2019 (COVID-19) pandemic affected mortality of patients with CLD both directly, with a higher risk for severe illness and death depending on age, stage and etiology of the disease, and indirectly, through social isolation and loss of support, harmful drinking, and difficulties in access to care. Nevertheless, only sparse data are available on variations in CLD as a cause of death during the pandemic. In the USA, in 2020-2021 a growth in mortality was registered for all liver diseases, more marked for alcoholic liver disease, especially among young people aged 25-44 years and in selected ethnic groups. COVID-19 related deaths accounted only for a minor part of the excess. Further data from mortality registers of other countries are warranted, preferably adopting the so-called multiple cause-of-death approach, and extended to deaths attributed to viral hepatitis and liver cancer.

Key Words: Mortality; Multiple causes of death; COVID-19; Chronic liver disease; Liver

cirrhosis; Liver cancer

Core tip: Preliminary data on causes of death during the coronavirus disease 2019 pandemic suggest that mortality from chronic liver disease (CLD) increased especially in countries where the alcoholic etiology was predominant, or with a prepandemic growing trend in mortality from alcoholic liver disease. Population-based studies on the direct and indirect effects of the pandemic on CLD mortality are strongly warranted. Analyses adopting the multiple cause-of-death approach might be better suited to fully investigate the impact of the pandemic on complex long-term pre-existing trends.

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INTRODUCTION

According to a systematic analysis of the Global Burden of Disease (GBD) Study 2017, deaths from cirrhosis and other chronic liver diseases (CLDs) were estimated at 1.32 million in 2017, compared to 889 000 in 1990. However, the corresponding age-standardized rate decreased from 21.0 to 16.5 per 100000 population. Rates decreased or remained constant in all regions except for Eastern Europe and Central Asia. Globally, age-standardized death rates associated to all main etiologies (alcohol, hepatitis B, and hepatitis C) declined, except for nonalcoholic steatohepatitis[1].

However, interpretation of mortality data on CLD poses several challenges. Cirrhosis mortality captures only a limited fraction of deaths due to CLD. In the USA, by adopting the standard definition for CLD mortality, a 38% decrease in rates was observed from 1979 to 2008; if other liver-related causes of death including viral hepatitis and liver cancer were examined, rates remained essentially unchanged[2]. Liver cirrhosis mortality dropped, whereas death rates for primary liver cancer were stable in Northeastern Italy in 1995-2010[3], and increased in China in 1987-2016[4]. A more comprehensive assessment on mortality from CLD can also be achieved by analyses not limited to the underlying cause of death, but extended to all conditions mentioned in death certificates. The so-called multiple cause-of-death approach can unveil rapidly changing trends limited to specific etiologies within selected birth cohorts. As an example, a rise in mortality related to hepatitis C virus (HCV) was registered in the USA in 2003-2013; most deaths were confined to the 1945-1965 birth cohort, affected by the highest prevalence of HCV infection[5]. A similar growth in HCV-related mortality within a specific birth cohort was observed in Northern Italy[6]. After 2014, time trends in the USA changed and mortality related to HCV started to decline, whereas death rates related to alcoholic liver disease and nonalcoholic fatty liver disease (NAFLD) were on the rise[7].

In the most recent years, patients with CLD represented a vulnerable population during the coronavirus disease 2019 (COVID-19) pandemic due to immune dysregulation and coagulopathy among those with advanced disease, and coexisting comorbidity, including obesity, diabetes and cardiovascular diseases. Notably, baseline liver disease stage and alcoholic liver disease were demonstrated to be independent risk factors for death from COVID-19[8]. Nevertheless, to date, population-based data on trends in CLD as a cause of death during the pandemic are lacking, except for an increase in mortality from liver cirrhosis reported from the USA already in its early phases[9]. We review here the available evidence on the impact of the pandemic on pre-existing time trends in mortality from CLD.

MORTALITY TRENDS BEFORE THE PANDEMIC

In 2017, there were 2.14 million estimated liver-related deaths; liver cirrhosis and liver cancer accounted for 61.7% and 38.3%, respectively. Between 2012 and 2017 the global age-standardized death rate increased (annual percent change, APC = 0.51%, 0.05%-0.98%) for liver cancer and decreased (APC = 0.70%, 1.01% to 0.40%) for liver cirrhosis. In Asia, the most common cause was hepatitis B virus (HBV) infection (highest in East Asia), whereas HCV was the most common cause in high-income Asia Pacific and Middle East and North Africa (MENA), and alcohol-related liver disease in Central Asia. Incidence and mortality associated with NAFLD increased globally, and this increase was recorded in almost every region worldwide[10].

Hepatitis B is the leading etiology for liver cancer mortality and the third largest contributor to deaths from cirrhosis. HBV-related diseases resulted in 555 000 global deaths in 2019; the number of HBV-related deaths increased between 1990 and 2019. By contrast, age-standardized death rates declined globally and in all world regions. Meanwhile, there was a 31.3% decrease in the prevalence of HBV at all ages[11]. Mortality trends related to hepatitis C are less pronounced; in 2010-2019 the decline in mortality was larger for acute hepatitis C than for HCV-related cirrhosis, with no significant change for HCV-related liver cancer[12].

A number of studies addressed global trends in liver cancer incidence and mortality. According to the GBD 2015 study, globally, HBV accounted for 33% of a total of 810 000 liver cancer deaths, alcohol for 30%, and HCV for 21%. The highest share for HBV was observed in Western sub-Saharan Africa, East Asia, and Andean Latin America; that for HCV in high-income Asia Pacific, MENA, Central and Southern Latin America, and Western Europe; and that for alcohol in Central and Eastern Europe. From 1999 to 2015, age-standardized mortality rates declined substantially in regions with high liver cancer burden such as East Asia and sub-Saharan Africa, probably due to the effect of primary liver cancer prevention through HBV vaccination[13]. These trends parallel those in liver cancer incidence. The burden in highly endemic regions has been partially alleviated due to improved control of viral hepatitis, especially among young and middle-aged people. By contrast, an unfavorable trend was observed in most developed countries and in older populations[14]. In fact, the most significant increases in incidence were generally observed in countries with a high sociodemographic index, including the UK and the USA[15]. Nevertheless, chronic HBV and HCV remain important risk factors for liver cancer. Based on the GLOBOCAN database, the overall increasing trend in incidence and mortality from liver cancer was confirmed among older male subjects, and in countries with a higher prevalence of HCV-related liver cancer. The increasing prevalence of alcohol consumption and obesity may have contributed to this epidemiological scenario in high-income countries[16].

As regards mortality from liver cirrhosis, analyses of the GBD 2017 study showed that deaths due to cirrhosis constituted 2.4% of total deaths globally. Central Asia had the highest age-standardized death rate, followed by Sub-Saharan Africa. Central Asia and Eastern Europe were the only two regions in which mortality rates significantly increased during 1990-2017; in both, prevalent cases were predominantly caused by alcohol-related liver disease. At the national level, the highest mortality rate was registered in Egypt, whereas the steepest growth was observed in Lithuania. Deaths from cirrhosis in males were mostly attributed to hepatitis B (31.5%), alcohol (27.3%), and hepatitis C (25.5%); the corresponding percentages in females were 24.0%, 20.6%, and 26.7%[1].

In view of the above, prepandemic global patterns in CLD mortality differed according to cause of death (liver cirrhosis or liver cancer), etiology, and world region (Figure 1). Furthermore, even within a single country, different patterns of mortality could be registered according to complex interactions between demographic characteristics (sex, age group, ethnicity, and socioeconomic status) and etiology of liver disease. Mortality from CLD overall, and especially that from alcoholic liver disease, is in fact strongly associated with socioeconomic status[17]. Different trends in CLD mortality by etiology have been investigated in the USA by means of the multiple cause-of-death approach. Overall, an increase in mortality from cirrhosis and hepatocellular carcinoma has been registered in the prepandemic period[18]. However, drastically different trends were observed according to etiology. HCV-related mortality increased from 2007 to 2014 and sharply declined in 2014-2016, after the introduction of direct-acting antiviral therapies; meanwhile, a decrease in HBV-related mortality, and an increase in alcoholic liver disease and NAFLD mortality was observed in 2007-2016. Minorities were disproportionately affected, especially non-Hispanic blacks by HCV-related mortality and Asians by HBV-related mortality[7]. An increase in mortality related to NAFLD was confirmed by other authors in the same period, especially among older subjects, females, non-Hispanic whites, and American Indian/Alaskan Natives[19].

CLD AND COVID-19

Although COVID-19 primarily affects the respiratory system, causing pneumonia and acute respiratory distress syndrome in severe cases, it can also result in multiple extrapulmonary complications. The pathogenesis of extrapulmonary damage in patients with COVID-19 is probably multifactorial, involving both the direct effects of SARS-CoV-2 and the indirect mechanisms associated with the host inflammatory response[20]. Research has shown that COVID-19 can cause liver injury due to inflammation, which can lead to liver damage or failure, particularly in people with pre-existing liver conditions such as cirrhosis. People with COVID-19 who have pre-existing liver conditions may be at a higher risk for severe illness and death[21]. For these reasons, they should always continue to follow their treatment plan and keep in close contact with their healthcare provider.

Etiology of liver disease and COVID-19 impact

It is reported that liver diseases of viral etiology are not associated *per se* with the severity or outcome of COVID-19, and this finding has been consistent across Asia, Europe and the USA. According to recent data from the European Reference Network for Rare Liver Diseases, autoimmune liver diseases and the related immunosuppressive therapy do not represent a specific risk factor for COVID-19, and the risk, as with other etiologies, is determined by the stage of cirrhosis [22]. Several studies highlighted the presence of severe complications in patients with SARS-CoV-2 infection and metabolic-syndrome-associated comorbidities, including NAFLD. The shared genetic influence between COVID-19 susceptibility and NAFLD, the sex-linked and the liver single-cell differential expression level of diverse transcripts and biological pathways might uncover shared disease mechanisms that explain the severe complications and increased in-hospital mortality risk associated with comorbidities, including NAFLD[23]. Lockdown, economic hardship, and the psychological impact of the pandemic all had a detrimental effect on people with liver disease, including poorer metabolic control in people with metabolic syndrome and fatty liver disease. This likely had deleterious consequences on the liver and cardiovascular outcomes of people with NAFLD, particularly those with advanced liver disease. Mortality has been shown to increase in people with alcohol-associated liver disease[24].

The role of cirrhosis

Prospective data from multicenter studies confirmed that patients with cirrhosis, particularly those who are

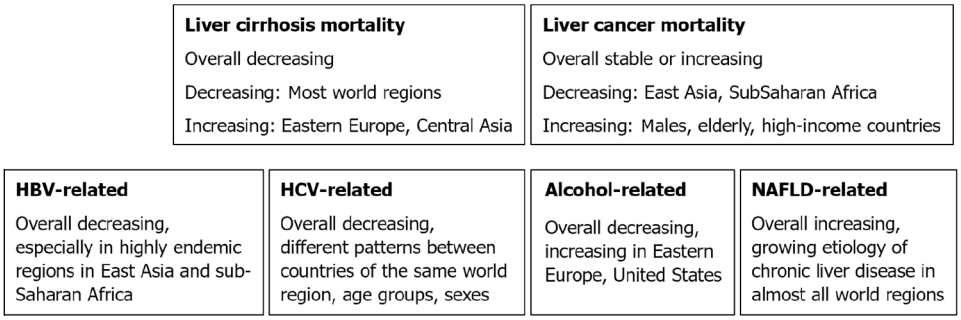

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Figure 1 Trends in mortality from liver diseases before the pandemic, by cause of death and etiology. HBV: Hepatitis B virus; HCV: Hepatitis C virus; NAFLD: Nonalcoholic fatty liver disease.

decompensated, are at a higher risk of hospitalization, ventilation and death than those without CLD. Older age and cirrhosis severity, as assessed by Child-Pugh class, are the most important predictors of mortality[25]. Overall mortality in patients with cirrhosis following SARS-CoV-2 infection was 32% in a large registry cohort of 729 predominantly hospitalized patients with CLD across 29 countries, with case-fatality rates incrementally increasing with each Child-Pugh class (CLD without cirrhosis 8%; class A 19%; class B 35%; class C 51%). The multivariable analysis of factors associated with death demonstrated persisting positive associations with age [odds ratio (OR) 1.02; 95% confidence interval (CI) 1.01-1.04; $P = 0.011$], the different stages of cirrhosis compared with CLD without cirrhosis (Child-Pugh class A, OR 1.90; 95%CI: 1.03-3.52; $P = 0.040$; class B, OR 4.14; 95%CI: 2.4-7.65; $P < 0.001$; and class C, OR 9.32; 95%CI: 4.80-18.08; $P < 0.001$), and alcoholic liver disease (OR 1.79; 95%CI: 1.03-3.13; $P = 0.040$)[8].

Patients with CLD and especially cirrhosis, have multiple mechanisms of immune dysfunction that can lead to increased susceptibility to infection and an aberrant inflammatory response during infection, collectively known as cirrhosis-associated immune dysfunction[26]. This immune dysfunction includes reduced components of the complement system, macrophage activation, impaired lymphocyte and neutrophil function, Toll-like receptor upregulation, and intestinal dysbiosis[27].

The role of vaccination

By April 2022, more than half of the world's population had received at least one vaccine dose, with real-world data showing that vaccination is generally safe and significantly reduces mortality. However, the initial high efficacy against infection has decreased following the emergence of new SARS-CoV-2 variants. Vaccine efficacy is particularly low against the Omicron variant, although fortunately it still confers considerable protection against severe COVID-19[28,29]. Although vaccines and previous infections largely protect against severe clinical courses of COVID-19, particularly in the current phase of the pandemic, which is dominated by sublineages of the SARS-CoV-2 Omicron variant, there is still a significant unmet medical need for therapeutics to treat severe disease in unvaccinated or older patients and patients with chronic disease conditions[30]. The impact of liver disease severity on vaccine efficacy should be convened to patients, so that they are aware of their increased risk and continue to take personal protective measures[31].

CLD AS A CAUSE OF DEATH DURING THE COVID-19 PANDEMIC

Between 2012 and 2019, rates of alcohol-specific deaths in the UK remained stable, whereas during the pandemic years, they rose from 11.8 per 100000 in 2019 to 14.8 in 2021. Alcoholic liver disease accounted for 78% of alcohol-specific mortality: the number of registered deaths grew from 5840 in 2019 to 7518 in 2021. This rise was attributed to increased alcohol consumption during the pandemic. Although alcoholic liver disease takes many years to develop, a further increase in alcohol intake among high-risk consumers can lead to rises in mortality in a short period of time, from what is known as acute-on-chronic liver failure[32].

In Minnesota, USA, an increase in both alcoholic liver disease and cirrhosis/other CLD as the underlying cause of death was registered in 2020 with respect to 2018-2019[33]. The growth in deaths from alcoholic liver disease as the underlying cause was confirmed at the national level[34]. According to analyses of national US multiple cause-of-death data, during the first year of the COVID-19 pandemic, the pre-existing growing trend in alcoholic liver disease mortality further accelerated, with the quarterly increase rising from 1.1% to 11.2%. Similarly, the quarterly increase in NAFLD grew from 1.9% to 6.6%. Mortality related to HBV and HCV, previously declining in the prepandemic period, remained stable[35]. Similar analyses were extended to 2021 data from the USA, confirming the increase through the second year of the pandemic for all liver diseases. This was more marked for alcoholic liver disease, especially among the young population aged 25-44 years and in selected ethnic groups such as American Indian/Alaskan Natives. The decline in HCV-related mortality observed since 2014 slowed down[36]. Years of potential life lost from premature deaths (< 65 years) attributable to cirrhosis listed as one of the causes of death in US certificates grew by 20.7% in 2020 and by 29.5% in 2021. COVID-19-related deaths accounted only for a minor part of such excess. Again, the increase was more pronounced for the alcoholic etiology, consistent with growing alcohol sales in the USA during the pandemic[37]. Patients with

alcoholic liver disease might have disproportionally suffered from a surge in harmful drinking, social isolation, and loss of familial and social support, along with barriers to access to outpatient clinics and rehabilitation services. Another study of US national multiple cause-of-death data reported a marked increase in mortality from CLD and/or cirrhosis among decedents with mention of diabetes, specifically associated with increased mortality from NAFLD and alcohol-related liver diseases[38].

By contrast in Spain, no major change in the number of deaths from CLD in 2020 compared to the 2018-2019 average was observed, based both on the underlying cause of death (0.9%) and on multiple cause-of-death data (+3.1%)[39].

In view of the paucity of published evidence outside the USA, we retrieved mortality rates for liver cirrhosis (International Classification of Diseases-10th Revision codes K70 and K74) from the World Health Organization (WHO) mortality database (https://platform.who.int/mortality). Table 1 shows countries with data updated at least until 2020; few had data available for the year 2021. In 2020 a large increase was registered in the USA (+18% with respect to 2019) and the UK (+16%). Among the other most populous countries, rates in the Americas were almost unchanged (Mexico, Brazil and Argentina) or declined (Peru and Colombia). European countries showed no increase (Spain) or only a limited mortality increase (Germany and Poland). Rates decreased in Malaysia and showed only minor growth in other Asian countries (Kazakhstan, Japan and Korea) and in Australia. Among less populous countries, a marked increase was registered in some Eastern European countries: Estonia, Lithuania, and in 2021 Latvia, Czechia and North Macedonia. A more comprehensive evaluation will however be possible when complete 2021 data become available, in consideration of how the pandemic involved different world regions in subsequent phases (*e.g.*, Central and Eastern Europe were more severely affected in 2021 compared to 2020). Additional nationwide data not included in the WHO database can be retrieved from institutional websites. As an example, in Italy age-adjusted mortality rates from liver cirrhosis, fibrosis and chronic hepatitis in 2020 showed a 3% reduction with respect to 2019, which is consistent with the decreasing trend observed in recent years (http://dati.istat.it/). Mortality from liver cirrhosis more closely parallels mortality from alcoholic liver disease with respect to that associated with other etiologies, and analyses including codes for viral hepatitis and liver cancer are warranted[3]. Lastly, also due to coding rules set by WHO[40], COVID-19 itself may have acted as a competing condition for the selection as the underlying cause of death in patients affected by pre-existing chronic diseases[35].

CONCLUSION

A large variation in trends of mortality from CLD was observed at the global level before 2020. Based on the few available published reports, the COVID-19 pandemic had a different impact depending on the local epidemiological context. Probably, mortality from CLD increased, especially in areas where the alcoholic etiology was predominant, or where a growing trend in mortality from alcoholic liver disease was already in place. Therefore, population-based studies on the direct and the indirect effects of the COVID-19 pandemic on CLD mortality are strongly warranted. Analyses adopting the multiple cause-of-death approach, and extended to deaths attributed to viral hepatitis and liver cancer, might be better suited to fully investigate the impact of the pandemic on complex long-term pre-existing trends.

Table 1 Age-standardized mortality rates (×100000) from cirrhosis, World Health Origination mortality database

	2021	2020	2019	2018	2017	2016	2015	2014	2013	2012
Antigua-Barbuda		3.4	2.7	4.5	3.6	0.9	2.9	6.8	1.9	10.1
Argentina		6.7	6.6	7.0	7.2	8.3	7.9	6.8	6.5	6.5
Armenia	10.9	12.2	10.6	12.0	16.0	19.5	16.6	17.1	14.9	16.5
Australia	4.6	4.3	4.1	4.0	4.0	3.7	4.1	3.9	3.9	3.3
Austria	8.6	8.5	8.1	7.9	8.4	9.0	9.5	9.4	9.9	10.7
Bosnia-Herzegovina		5.4	5.0	4.8	5.1	5.6		5.9		
Brazil		8.0	8.1	8.4	8.8	9.2	9.3	9.4	9.8	10.0
Bulgaria		15.6	15.8	14.3	14.5	14.8	14.4	13.4	13.1	13.8
Chile		9.7	9.4	9.9	11.3	12.4	11.7	11.8	12.3	13.5
Colombia		4.6	5.1	5.1	5.1	5.4	5.2	5.1	4.8	4.8
Costa Rica		5.2	6.9	6.2	6.3	6.3	6.5	6.1	6.2	5.2
Croatia		11.4	13.0		12.5	12.1	12.4	13.7	13.3	14.8
Cuba		10.8	10.5	10.0	9.8	9.0	8.9	8.5	8.2	7.9
Cyprus		3.6	3.9	3.2	3.2	2.7	3.2	3.6	4.0	2.8
Czechia	13.8	12.4	12.4	12.0	11.8	10.7	11.2	11.2	11.5	11.5

Denmark		6.7	7.2	6.5	7.2	7.1	6.7	7.6	7.6	8.4
Ecuador	12.5	11.8	13.2	13.7	14.0	14.6	14.5	13.3	13.1	13.7
Estonia	24.9	22.0	17.1	16.1	14.7	15.3	15.8	14.0	13.4	12.4
Finland		13.7	12.5	11.9	11.4	12.5	12.1	13.7	14.4	14.3
Georgia	7.2	7.0	7.0	7.5	5.6	5.5	7.4	8.0	6.0	6.4
Germany		9.2	8.7	8.9	9.1	9.3	9.1	9.0	9.5	9.3
Greece		3.3	3.3	3.1	3.5	3.6	3.6	3.7	4.1	3.8
Grenada	1.4	6.3	3.7	7.1	6.4	8.4	9.9	10.1	7.2	7.0
Guatemala		29.5	29.6	29.4	28.3	32.7	31.8	31.2	29.0	29.2
Iceland	2.7	1.8	1.4	1.9	2.5	1.6	2.7	1.5	1.7	1.4
Israel		2.0	2.5	2.4	2.3	2.5	2.7	2.3	2.7	2.8
Japan		4.9	4.7	4.7	4.7	4.4	4.4	4.5	4.7	4.7
Kazakhstan	38.6	40.2	38.5	38.5	41.4	46.4	50.5	55.2	57.9	
Latvia	18.9	12.4	12.1	13.6	11.5	13.6	12.8	12.5	12.6	12.4
Lebanon	2.6	2.1	1.9							
Lithuania	20.6	19.6	15.3	15.9	16.4	19.1	18.7	19.7	22.8	21.2
Luxemburg	7.0	7.8	7.2	8.0	7.2	8.9	6.7	8.0	7.5	9.1
Malaysia		1.7	2.0	2.0	1.8	1.8	2.0	1.9	1.8	1.7
Mauritius	10.9	10.7	8.6	7.9	8.0	8.8	8.9	8.9	10.3	9.7
Mexico		25.5	24.5	24.4	25.3	26.1	24.2	24.1	25.4	26.0
Mongolia	25.9	24.5	27.2	28.9	31.0	35.6				
Netherlands		3.0	2.7	2.8	2.9	2.9	2.8	2.7	2.6	2.9
Nicaragua		15.4	15.6	19.9	19.8	23.0	20.7	23.0	22.0	19.1
North Macedonia	6.9	5.0	4.9	4.7	6.0	5.2	5.9		6.3	5.4
Oman	1.5	1.5	2.0	1.5	2.6	2.2		1.6		
Paraguay		6.4	8.1	8.4	7.4	8.2	7.5	7.1	6.3	6.6
Peru		12.1	13.2	14.2	12.6	11.1	12.4	11.9	11.4	12.8
Poland		14.5	13.5	13.3	12.3	11.6	10.7	10.4	11.2	12.0
Qatar	1.6	2.1	1.2		2.9	1.8	0.6	1.7	1.2	2.1
Republic of Korea		7.1	6.8	7.3	7.5	7.8	8.1	8.0	8.3	8.8
Saint Lucia		3.7	3.6	6.2	4.2	5.9	8.9	12.1	7.9	9.1
Saint Vincent	3.1	4.5	5.6	6.9	5.7	4.9	2.5	5.4	7.0	7.2
Serbia	6.3	5.8	5.8	5.2	5.7	5.5	5.7	5.7	5.6	5.9
Singapore		1.7	2.2	2.2	2.3	2.4	2.2	2.6	2.5	2.4
Slovenia		9.9	10.2	10.9	9.6	9.9	11.4	13.5	16.2	17.9
Spain	4.6	4.4	4.5	4.6	4.9	4.9	5.4	5.3	5.6	5.8
Switzerland		3.6	3.8	3.9	3.9	4.1	4.4	4.4	4.5	5.0
United Arab Emirates		1.8	1.9	0.0						
UK		9.4	8.1	8.2	8.5	8.4	8.2	8.1	8.1	8.0
USA		10.9	9.2	9.0	8.9	8.7	8.8	8.5	8.2	8.0
Uruguay		3.3	3.0	3.3	3.3	3.7	4.3	4.4	3.8	3.9

FOOTNOTES

Author contributions: Fedeli U designed the outline, coordinated the writing of the paper, prepared figures/tables; Barbiellini Amidei C,

Casotto V, Grande E, Saia M, Zanetto A, and Russo FP collected the relevant bibliography and wrote the sections of the review; Barbiellini Amidei C and Casotto V contributed to "trends before the pandemic"; Zanetto A and Russo FP contributed to "COVID-19 and CLD"; Grande E and Saia M contributed to "CLD as a cause of deaths during the pandemic"; and all authors contributed to revising the first draft and approved the final version of the manuscript.

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