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Decline in Complications and Mortality in Chronic Liver Disease and Cirrhosis: A Population-Based Cohort Study From Northeastern Italy

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ABSTRACT

Background: Current trends in complications and mortality among individuals with chronic liver disease and cirrhosis are largely unknown.

Objective: To explore changes in mortality trends among patients with cirrhosis and chronic liver disease based on etiology in the Veneto Region (Italy), to differentiate mortality between liver-related and non-liver-related causes before and during the COVID-19 pandemic, and to determine trends in the development of cirrhosis complications.

Methods: Three subsequent population-based cohorts of individuals with chronic liver disease/cirrhosis were identified in Veneto (North-eastern Italy, 4.9 million residents): the first enrolled before introduction of direct-acting antivirals (DAA); the second corresponding to full availability of DAA treatment; and the last enrolled at the beginning of the pandemic. Risks of liver decompensation and death—liver and non-liver related—were recorded for each cohort during a 3-year follow-up. Changes in the risk of death across cohorts were measured by risk ratios (RR) obtained through Poisson regression models with robust error variance.

Results: Across the cohorts spanning over 10 years, we found that the number of individuals with CLD and cirrhosis remained stable at about 40,000 and 10,000, respectively. The 3-year risk of ascites, hepatic encephalopathy, and hepatocellular carcinoma decreased across the study period, largely due to individuals with HCV-related liver disease. The overall 3-year mortality risk declined by 14% (liver cirrhosis, subjects enrolled in 2020 vs. 2013: RR = 0.86, 95% CI 0.83–0.89), especially among those with viral etiology. In contrast, mortality due to alcohol-related chronic liver disease/cirrhosis was stable or increasing during the COVID-19 pandemic, especially for non-liver causes of death.

Abbreviations: CI, confidence intervals; CLD, chronic liver disease; DAA, direct-acting antivirals; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD 9-CM, international classification of diseases revision, ninth revision, clinical modification; MASLD, metabolic dysfunction-associated steatotic liver disease; RR, risk ratio.

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Conclusions: Despite increased awareness and proactive enrollment into patient care, chronic liver disease and cirrhosis remain significant health-challenges. The reduction in HCV-related mortality underscores the impact of antiviral treatments, while the persistently high mortality risk of alcohol-related disease highlights the need for targeted interventions.

1 | Introduction

Chronic liver disease (CLD) is reported to be the 14th most common cause of death globally [1] despite a possible underestimation [2]. In Europe, mortality due to CLD is increasing [3, 4]. Contrary to diseases related to smoking or obesity, for which deaths mostly occur later in life (at around 60–70 years), CLD has a significant impact on young and middle-aged individuals in working ages, with deaths occurring already in the late 40s and early 50s. In fact, CLD is the 2nd leading cause of years of working life lost in Europe, contributing to a significant economic and health burden [3, 4]. These trends should be interpreted within the recent COVID-19 pandemic [5]. A substantial variation in trends of mortality from CLD was registered globally before 2020. During the COVID-19 pandemic, mortality from CLD increased in areas where alcohol-related etiology was predominant or an increase in alcohol-related CLD mortality was already in place [6].

In patients with CLD, most deaths can be attributed to the development of cirrhosis and its complications such as ascites, variceal bleeding, and hepatic encephalopathy [7]. Cirrhosis is a multifaceted condition characterized by progressive liver scarring and impairment of liver function with development of portal hypertension [8]. Mortality risks in individuals with cirrhosis and its determinants have long been investigated by healthcare professionals, researchers, and policymakers [9].

It bears noting that the natural history of cirrhosis is characterized by two main stages: compensated and decompensated cirrhosis, which are two distinct entities with different clinical course and prognosis. Decompensation is defined by the occurrence of ascites, portal hypertensive gastrointestinal bleeding, hepatic encephalopathy, or jaundice [10]. Notably, the median survival of patients with compensated cirrhosis is as long as 10–12 years, with death occurring mostly after decompensation, whereas the median survival of decompensated patients is about 2 years [11, 12]. The Baveno VII expert consensus suggests that, in some patients who achieve etiological cure, decompensated cirrhosis may recompensate [7]. However, in most cases, cirrhosis represents the "end-stage" condition of various chronic liver diseases, including chronic viral hepatitis B/D and C, alcohol-related liver disease, and metabolic dysfunction-associated steatotic liver disease (MASLD).

Besides the development of hepatic decompensation, etiology of CLD is emerging as a key determinant of both morbidity and mortality. On the one hand, patients with alcohol-related cirrhosis may face distinct challenges compared to those with viral-related aetiologies, likely requiring tailored approaches to improve prognosis and management [13]. On the other hand, the recent introduction of direct-acting antivirals (DAAs) has significantly accelerated the pre-existing decline in hepatitis C virus (HCV)-related mortality in the general population and halted the increase in deaths associated with HCV in the high-risk birth cohort of the 1960s [14, 15]. Finally, the high prevalence of diabetes and obesity in Europe and in the United States contributes to the increasing burden of MASLD, which is the leading cause of hepatocellular carcinoma (HCC) and the first indication for liver transplantation [16].

A thorough investigation of adverse outcomes and mortality of CLD and cirrhosis may improve not only our understanding of this challenging disease but also help to plan the next actions, at a national and international level, to mitigate the enormous healthcare burden associated with these conditions [3, 4].

This study aimed to [1]: explore changes in mortality trends among patients with cirrhosis and CLD based on its etiology, in the Veneto Region in Italy [2]; disentangle mortality between liver and non-liver causes before and during the COVID-19 pandemic; and [3] determine trends in the development of cirrhosis complications.

2 | Materials and Methods

2.1 | Study Design

A population-based cohort study carried out in the Veneto Region (North-eastern Italy, about 4.9 million residents). To analyze changes in clinical outcomes across distinct intervals reflecting shifts in treatment resources and major changes in the healthcare system, such as the COVID-19 pandemic, we enrolled three consecutive cohorts of patients with CLD/cirrhosis. The first cohort was enrolled before the introduction of DAAs in Italy, the second during the period of full DAA availability for all HCV patients, and the third at the onset of the pandemic.

2.2 | Data Sources

All residents in Veneto aged 20–79 years identified through the archive of subjects enrolled in the Regional Health System were eligible for the study. To identify subjects affected by liver diseases and their outcomes, the database of residents (including information on age, gender, and country of citizenship) was linked to hospital discharge records, the healthcare co-payments exemptions database, and the regional mortality registry. Inpatient care is free of charge in Italy and is covered by general taxation. The healthcare co-payment exemption database includes information on all individuals with a diagnosis of selected chronic conditions, for which the national health service also provides specific outpatient care free of charge. Hospital discharge records contain data on all hospitalizations, including primary and secondary diagnoses, and any surgical or

Key Points

- Summarize the established knowledge on this subject:
  - Chronic liver disease is a global major health care concern, but the epidemiology of chronic liver disease in Italy is poorly known.
  - Understanding the evolving trends of outcomes and mortality in chronic liver disease will help plan the next actions to mitigate the healthcare burden associated with this condition.
- What are the significant and/or new findings of this study?
  - In Veneto region, Italy, the prevalence of chronic liver disease and cirrhosis has remained stable over the past decade.
  - The incidence of ascites, hepatic encephalopathy, and hepatocellular carcinoma has decreased over the last 10 years, primarily due to the reduced burden of HCV.
  - In contrast to chronic viral hepatitis, mortality from alcohol-related chronic liver disease and cirrhosis has remained stable or increased, highlighting the necessity for focused preventive measures and treatment strategies.

medical procedures performed during the hospitalization. All discharge diagnoses are coded according to the International Classification of Diseases Revision, Ninth Revision, Clinical Modification (ICD 9-CM). The regional mortality records include data on all residents' deaths, regardless of the place of death; causes of death are coded using the ICD-10. These systems are used nationwide as per ministerial regulation (https://www.pnrr.salute.gov.it/portale/assistenzaOspedaliera/homeAssistenzaOspedaliera.jsp).

2.3 | Cohorts of Subjects With CLD and Study Outcomes

Three cohorts were recruited on January 1st of the years 2013, 2017, and 2020, including all residents with either an active copayment exemption for cirrhosis (exemption code 008), active chronic hepatitis (code 016), primary sclerosing cholangitis (code RI0050), or with at least one hospitalization in the preceding 5 years with a primary or secondary diagnosis of liver diseases (ICD 9-CM 070.2x, 070.3x, 070.41, 070.42, 070.44, 070.51, 070.52, 070.54, 070.59, 070.7x, 070.9, 571.0, 571.1, 571.2, 571.3, 571.4, 571.5, 571.6, 571.8, 571.9). Liver diseases have been classified, based on etiology, into hepatitis B virus (HBV)-related (ICD 9-CM 070.2x, 070.3x, 070.42, 070.52), HCV-related (ICD 9-CM 070.41, 070.44, 070.51, 070.54, 070.7x), and alcohol-related (ICD 9-CM 571.0, 571.1, 571.2, 571.3). For each of the three study cohorts, a follow-up period of 3 years was considered as follows: January 2013–December 2015 for the cohort enrolled on January 1st, 2013; January 2017–December 2019 for the cohort on January 1st, 2017; January 2020–December 2022 for the cohort on January 1st, 2020. According to the study design, subjects surviving at the end of the follow-up period could be recruited into the subsequent cohorts, but the follow-up periods were not overlapping. Study outcomes were death from any cause, and the occurrence of severe complications: hospital admission for ascites (ICD 9-CM: 789.5), bleeding from esophageal varices (ICD 9-CM: 456.20), hepatic coma (ICD 9-CM: 572.2), spontaneous bacterial peritonitis (ICD 9-CM: 567.23), hepatorenal syndrome (ICD 9-CM: 572.4), hepatocellular carcinoma (ICD 9-CM: 155.0), or liver transplantation (ICD 9-CM intervention code: 50.5x). Mortality was analyzed both overall and broken down into liver-related and non-liver-related based on the underlying cause of death coded in the mortality register. According to previous studies [17], liver-related deaths included viral hepatitis, liver cancer, cirrhosis, and other liver diseases (ICD 10 codes B15-B19, C22.x, I85.x, K70-K76).

2.4 | Statistical Analysis

For each study cohort, the point prevalence was calculated as the ratio between the number of enrolled cases and the resident population in the Region on January 1, 2013, 2017, and 2020. Prevalence rates per 1000, along with 95% confidence intervals, were computed for each cohort stratified by etiology, age, sex, and immigrant status (residents with Italian vs. foreign citizenship).

Study outcomes (mortality and severe complications) were investigated by calculating 3-year risks, with prevalent cases on January 1st of each cohort as the denominator. Risks were computed for the entire cohort, and by etiology. Direct standardization by age and sex was performed using the demographic distribution of all prevalent CLD cases on January 1st, 2013 as a reference. To assess variations in standardized risks of death in the 2017 and 2020 cohorts compared with the 2013 cohort, risk ratios (RR) with 95% confidence intervals (CI) were calculated by Poisson regression models with robust error variance using SAS GENMOD (version 9.4, SAS Institute Inc.). All analyses were carried out on all subjects with CLD and were restricted to those with a diagnosis of liver cirrhosis at the time of enrollment (exemption code 008 or at least one hospitalization with ICD 9-CM diagnosis 571.2, 571.5, 571.6 during the previous 5-years).

3 | Results

3.1 | Prevalence of CLD by Etiology

Overall, about 40,000 patients with CLD—of whom 10,000 were affected by cirrhosis—were identified in each of the three study cohorts (Table 1). Across the subsequent cohorts, the prevalence of HBV-related CLD increased from 1.5 to 2.2 per 1000 inhabitants, that associated with HCV remained stable (4.3 per 1000), while alcohol-related CLD (without viral hepatitis) declined from 1.9 to 1.5 per 1000. Over 70% of patients with alcohol-related CLD had a diagnosis of cirrhosis. In all subsequent analyses, subjects with both viral and alcohol-related CLD (about 400 in each cohort) were included in both etiology groups; the same was applied to about 250 patients with HBV/HCV coinfection.

Although remaining roughly stable in overall numbers, the demographic profile of HCV-related CLD changed over time.

Among males, a sharp peak in prevalence among middle-aged individuals could be observed, shifting from the 45–49 years age class in 2013 to the 55–59 years age class in 2020. Among females, the peak in the middle-aged population was much less evident, whereas rates were higher in the older age groups (Figure 1). The prevalence of HBV-related CLD was markedly higher among immigrants, with a sharp increase over time across all age classes. In the population with Italian citizenship, prevalence increased with age, with a slight decline over time among younger and a growth among older age classes (Figure 2). Details on numbers and prevalence rates of CLD by etiology, age class, sex, and Italian/foreign citizenship across the three cohorts are reported in the Supporting Information S1: Tables S1–S3.

3.2 | Complications and Mortality Risks

Among all subjects with CLD, the 3-year risk of any major complication declined across the three cohorts, with a pronounced drop in hospital admissions, especially for ascites and encephalopathy (Table 2). The overall burden on acute care hospitals markedly decreased: when lengths of hospital stays were summed across different complications within the three cohorts, they accounted for 70,176, 58,802, and 46,501 total hospital days in the 2013, 2017, and 2020 cohorts, respectively. Among patients with CLD, the 3-year risk of developing HCC decreased from 3.8% in the 2013 cohort to 3% in the 2020 cohort. Similarly, in patients with cirrhosis, the 3-year risk of HCC declined from 10.7% in 2013 to 9.2% in 2020. This reduction in 3-year HCC risk for both CLD and cirrhotic patients was largely due to a decline in HCC incidence among patients with HCV following the widespread use of DAAs: from 2.6% in 2013 to 1.8% in 2020 for CLD patients, and from 16.2% in 2013 to 10.2% in 2020 for cirrhotic patients. The 3-year risk of death decreased as well from 9.4% in the 2013 cohort to 8.3% in the 2017 cohort; thereafter, it remained stable at 8.2% in the 2020 cohort, whose follow-up spanned through the pandemic period (Table 2). Such improvement in outcomes could be observed only among subjects with HCV-related CLD. In analyses restricted to patients with a diagnosis of liver cirrhosis, complication and mortality risks were much higher, but time patterns were similar. Namely, the 3-year risk of hospital outcomes and all-cause mortality halved among subjects with HCV-related liver cirrhosis: the risk of death decreased from 26.4% in 2013 to 18.1% in 2017 and 13.9% in 2020 (Table 3). Figures on HBV-related cirrhosis were limited to low numbers, but a tendency could be observed towards reduced overall mortality, without a clear trend regarding hospitalization for major complications. Notably, mortality across subsequent cohorts remained unchanged for alcohol-related liver cirrhosis, with the 3-year risk of death remaining at about 26%–27%.

When mortality was broken down by cause, the reduction over time was more evident for death due to liver causes, especially among subjects with HCV; such finding was observed both in analyses including all CLD and in those restricted to patients with liver cirrhosis (Tables 4 and 5, respectively). A slight increase in non-liver causes of death among the 2020 liver cirrhosis cohort could be explained by the impact of the pandemic. Among cirrhotic patients with HCV, the mortality risk continued to decline during the pandemic due to the drop in deaths attributed to liver diseases. Among subjects with alcohol-related CLD, a relevant proportion of deaths was due to non-liver diseases, and mortality risks remained high over time irrespective of the cause of death. When age-sex standardized risks of all-causes of death were computed to account for the different demographics of the examined etiologies and for aging across the three cohorts of recruited subjects, the above findings on overall mortality were confirmed (Tables 4 and 5, Figure 3). The overall reduction in the risk of death was about 14% in the 2017 and 2020 cohorts compared with the 2013 cohort, both among all subjects with CLD and in those with liver cirrhosis (2020 vs. 2013, liver cirrhosis: RR = 0.86, CI 0.83–0.89). Such decline was more pronounced in patients with HCV, whereas the 3-year risk of death was unchanged—or slightly increased during the pandemic—in subjects with alcohol-related CLD.

4 | Discussion

Across the three cohorts spanning almost 10 years, we found that the numbers of CLD and cirrhosis were roughly stable. For HCV-related CLD, we observed a demographic shift in the peak prevalence occurring in middle age, reflecting the well-known burden of the 1960s birth cohort in Italy [14, 18]. The 3-year risk of ascites, hepatic encephalopathy, and other complications showed a decreasing trend over the study period, largely driven by reduction in cases with HCV etiology; a similar pattern was observed for hospitalization with HCC. The 3-year mortality risk among those with CLD and cirrhosis continued to decline also through the pandemic among subjects with HCV, whereas mortality from alcohol-related cirrhosis, after a slight decline, increased during the COVID-19 pandemic, especially for non-liver causes.

Several factors potentially contributed to the reduction in disease complications and hospital outcomes, even in the context of a stable or slightly increasing mortality in alcohol-related diseases. Firstly, the implementation of a strong regional awareness campaign and the development of an early referral network facilitated timely identification and management of patients with advanced liver disease through dedicated hub centers, likely improving clinical trajectories by earlier intervention and more coordinated care [19]. Secondly, the increased number of liver transplants, even in patients without 6 months of abstinence and/or in selected cases of acute-on-chronic liver failure at their first event of decompensation.

In spite of the well-recognized global impact of CLD a liver cirrhosis [3], difficulties in accessing granular data from individual countries and regions ultimately prevent a detailed evaluation of the healthcare burden associated with CLD [20]. Notably, studies on CLD prevalence estimated through routinely collected health archives have mostly been carried out in Canada [21]. Among recent European studies, in Aragona (Spain) estimates were only slightly lower than in Veneto [22], whereas a markedly lower prevalence was reported in Sweden [23]. Interestingly, we found that whereas the overall prevalence of CLD in Veneto was rather stable over time, that of HBV-

TABLE 1 | Number of subjects with chronic liver disease and prevalence rates in Veneto (Italy) on January 1st, 2013, 2017, and 2020, by sex, age, class, and etiology.

	January 2013			January 2017			January 2020		
	n	**Prev. × 1000**	**(95% CI)**	***n***	**Prev. × 1000**	**(95% CI)**	***n***	**Prev. × 1000**	**(95% CI)**
All patients with chronic liver disease									
All	40,164	10.9	(10.8–11.0)	39,545	10.8	(10.7–10.9)	40,959	11.2	(11.1–11.3)
Sex									
Males	24,505	13.5	(13.3–13.7)	23,893	13.2	(13.1–13.4)	24,614	13.6	(13.4–13.8)
Females	15,659	8.4	(8.3–8.5)	15,652	8.5	(8.3–8.6)	16,345	8.9	(8.7–9.0)
Age group (yrs)									
20–29	1102	2.3	(2.1–2.4)	1089	2.3	(2.2–2.4)	1042	2.2	(2.0–2.3)
30–39	3593	5.4	(5.2–5.6)	3019	5.3	(5.1–5.5)	3022	5.7	(5.5–5.9)
40–49	8905	10.7	(10.5–10.9)	7346	9.2	(9.0–9.4)	6618	8.9	(8.7–9.1)
50–59	9104	13.5	(13.2–13.8)	11,088	14.7	(14.4–15.0)	12,294	15.4	(15.1–15.6)
60–69	9171	16.1	(15.8–16.5)	8806	15.0	(14.7–15.3)	9617	15.9	(15.6–16.3)
70–79	8289	18.2	(17.8–18.6)	8197	17.1	(16.8–17.5)	8366	16.9	(16.6–17.3)
Etiology									
HBV	5356	1.5	(1.4–1.5)	6843	1.9	(1.8–1.9)	7910	2.2	(2.1–2.2)
HBV + HCV	264	0.1	(0.1–0.1)	227	0.1	(0.1–0.1)	194	0.1	(0.0–0.1)
HCV	15,293	4.2	(4.1–4.2)	15,583	4.3	(4.2–4.3)	15,653	4.3	(4.2–4.4)
Viral not specified	268	0.1	(0.1–0.1)	266	0.1	(0.1–0.1)	242	0.1	(0.1–0.1)
Alcoholic	7112	1.9	(1.9–2.0)	5597	1.5	(1.5–1.6)	5339	1.5	(1.4–1.5)
Other/unknown	11,871	3.2	(3.2–3.3)	11,029	3.0	(3.0–3.1)	11,621	3.2	(3.1–3.2)
Patients with cirrhosis									
All	10,076	2.7	(2.7–2.8)	9942	2.7	(2.7–2.8)	10,016	2.7	(2.7–2.8)
Sex									
Males	6415	3.5	(3.5–3.6)	6342	3.5	(3.4–3.6)	6469	3.6	(3.5–3.7)
Females	3661	2.0	(1.9–2.0)	3600	1.9	(1.9–2.0)	3547	1.9	(1.9–2.0)
Age group (yrs)									
20–29	45	0.1	(0.1–0.1)	46	0.1	(0.1–0.1)	47	0.1	(0.1–0.1)
30–39	197	0.3	(0.3–0.3)	164	0.3	(0.2–0.3)	155	0.3	(0.2–0.3)
40–49	1035	1.3	(1.2–1.3)	875	1.1	(1.0–1.2)	777	1.0	(1.0–1.1)
50–59	2347	3.5	(3.3–3.6)	2575	3.4	(3.3–3.5)	2539	3.2	(3.1–3.3)
60–69	3396	6.0	(5.8–6.2)	3271	5.6	(5.4–5.8)	3319	5.5	(5.3–5.7)
70–79	3056	6.7	(6.5–6.9)	3011	6.3	(6.1–6.5)	3179	6.4	(6.2–6.7)
Etiology									
HBV	368	0.1	(0.1–0.1)	458	0.1	(0.1–0.1)	540	0.1	(0.1–0.2)
HBV + HCV	51	0.0	(0.0–0.0)	44	0.0	(0.0–0.0)	48	0.0	(0.0–0.0)
HCV	1262	0.3	(0.3–0.4)	1659	0.5	(0.4–0.5)	1602	0.4	(0.4–0.5)
Viral not specified	17	0.0	(0.0–0.0)	16	0.0	(0.0–0.0)	17	0.0	(0.0–0.0)
Alcoholic	5091	1.4	(1.3–1.4)	4534	1.2	(1.2–1.3)	4488	1.2	(1.2–1.3)
Other/unknown	3287	0.9	(0.9–0.9)	3231	0.9	(0.9–0.9)	3321	0.9	(0.9–0.9)

Note: All patients and patients with cirrhosis. Alcoholic includes patients with alcoholic etiology only, excluding those with both alcoholic and viral CLD (424, 400, and 424 in 2013, 2017, and 2020, respectively) or cirrhosis (342, 371, and 406).

related CLD was increasing, reflecting the recent increase in immigrants from endemic areas such as Sub-Saharan Africa, Asia, and Eastern Europe [24]. Proactive interventions to establish easy access to hepatology care and follow-up for these individuals will be key in the near future to prevent the transmission of the HBV and development of its sequelae.

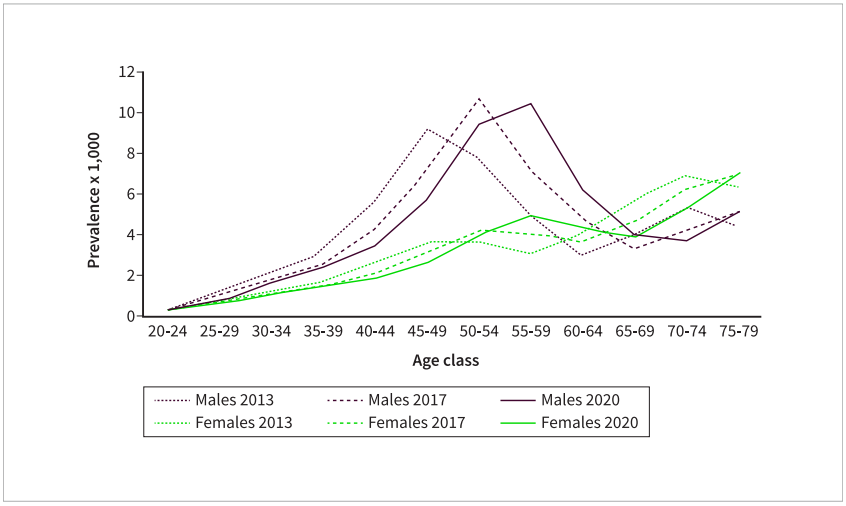

FIGURE 1 | Age and sex-specific prevalence of HCV-related chronic liver disease in January 2013, 2017, and 2020. Veneto region (Italy).

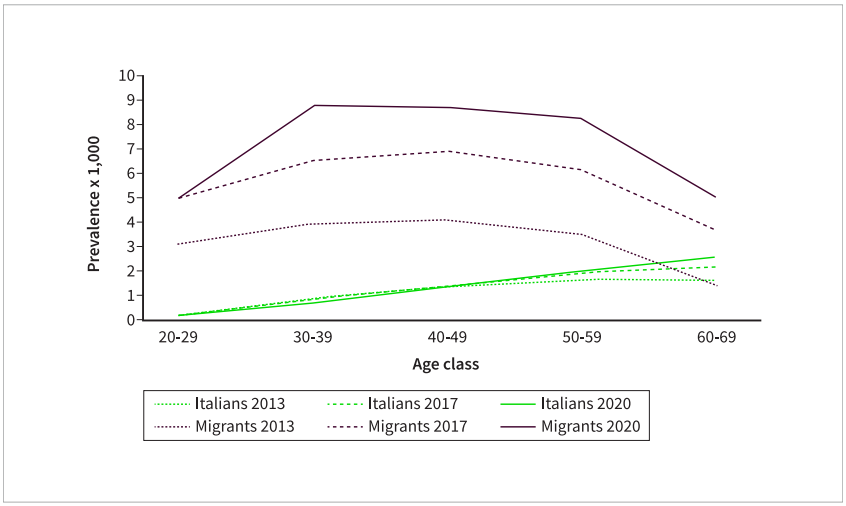

FIGURE 2 | Prevalence of HBV-related chronic liver disease by age class and Italian/migrant citizenship in January 2013, 2017, and 2020. Veneto region (Italy).

Regarding causes of death, liver-related causes declined, especially among individuals with HCV, but remained stable for alcohol-related CLD deaths. Non-hepatic related causes remained roughly stable if not slightly increased, especially during the COVID-19 pandemic among those with alcohol-related CLD. This finding underscores the importance of a multidisciplinary approach, as people with CLD, especially alcohol-related CLD, will more commonly die from causes that are not related to liver disease [25].

In epidemiological studies assessing the impact of CLD, it is paramount to separate between individuals with CLD and those with cirrhosis. As expected, we found that the risk of death and hospital admission due to liver-related causes was significantly higher in individuals with cirrhosis than in those with CLD. These results reinforce the recent recommendations by the EASL-Lancet Liver Commission for a more proactive screening and treatment of CLD in its early, asymptomatic stage, rather than solely focusing on the management of portal hypertension complications [3, 4]. Ascites was the most common decompensating event of CLD, independent of liver disease etiology, followed by hepatic encephalopathy, similar to recent data from Italy [26]. Variceal bleeding was less commonly observed, which may reflect a more widespread adoption of preventive measures aimed at reducing portal pressure in individuals with cirrhosis as well as strategies for prophylaxis [27]. A sensitivity analysis was carried out on all upper gastrointestinal bleedings; a reduced risk could be observed across the three cohorts, from 1.5% to 1.3% to 1.2% (data not shown).

Our study has significant limitations. Firstly, the use of electronic health archives may lead to coding biases and under notification of conditions. Alcohol-related CLD is especially likely underestimated due to the associated stigma; this might explain why as much as 70% of all alcoholic CLD in our study could be classified as cirrhosis. Secondly, there is no reliable code allowing the identification of MASLD, thus limiting our ability to evaluate the impact of this increasingly important liver condition in our cohort [28]. In future studies, a possible

TABLE 2 | 3-year risk of adverse outcomes among all subjects with chronic liver disease (CLD) enrolled in January 2013, 2017, and 2020 by etiology: Outcomes retrieved from hospital records (admission for ascites, variceal bleeding, encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatocellular carcinoma, liver transplant) and death from any cause.

				Hospital outcome:															
	Subjects enrolled	Any hospital outcome		Ascites		Variceal bleeding		Encephalpathy		Liver transplant		Spontaneous bacterial peritonitis		Hepatorenal syndrome		Hepatocellular carcinoma		Death	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	n	%	n	%
All CLD																			
2013	40,164	2822	7.0	1109	2.8	161	0.4	882	2.2	126	0.3	143	0.4	334	0.8	1508	3.8	3792	9.4
2017	39,545	2546	6.4	956	2.4	134	0.3	696	1.8	176	0.4	144	0.4	248	0.6	1457	3.7	3276	8.3
2020	40,959	2212	5.4	857	2.1	144	0.4	512	1.3	173	0.4	108	0.3	214	0.5	1235	3.0	3363	8.2
HBV																			
2013	5620	145	2.6	38	0.7	5	0.1	32	0.6	12	0.2	9	0.2	12	0.2	98	1.7	176	3.1
2017	7070	180	2.5	58	0.8	8	0.1	27	0.4	27	0.4	12	0.2	10	0.1	132	1.9	208	2.9
2020	8104	175	2.2	57	0.7	7	0.1	27	0.3	30	0.4	4	0.0	8	0.1	125	1.5	259	3.2
HCV																			
2013	15,557	662	4.3	250	1.6	33	0.2	186	1.2	50	0.3	34	0.2	65	0.4	399	2.6	879	5.7
2017	15,810	555	3.5	175	1.1	32	0.2	122	0.8	36	0.2	25	0.2	36	0.2	379	2.4	779	4.9
2020	15,847	404	2.5	124	0.8	28	0.2	67	0.4	32	0.2	14	0.1	23	0.1	279	1.8	744	4.7
Alcohol																			
2013	7536	1338	17.8	579	7.7	84	1.1	503	6.7	45	0.6	80	1.1	201	2.7	590	7.8	1702	22.6
2017	5997	1227	20.5	541	9.0	76	1.3	409	6.8	68	1.1	79	1.3	149	2.5	566	9.4	1383	23.1
2020	5763	1095	19.0	494	8.6	74	1.3	333	5.8	74	1.3	59	1.0	142	2.5	491	8.5	1439	25.0

TABLE 3 | 3-year risk of adverse outcomes among subjects with cirrhosis enrolled in January 2013, 2017, and 2020, by etiology: Outcomes retrieved from hospital records (admission for ascites, variceal bleeding, encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatocellular carcinoma, liver transplant), and death from any cause.

				Hospital outcome:															
	Subjects enrolled	Any hospital outcome		Ascites		Variceal bleeding		Encephalo-pathy		Liver transplant		Spontaneous bacterial peritonitis		Hepatorenal syndrome		Hepatocellular carcinoma		Death	
		N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
All cirrhosis																			
2013	10,076	2175	21.6	899	8.9	139	1.4	759	7.5	103	1.0	115	1.1	291	2.9	1080	10.7	2350	23.3
2017	9942	1970	19.8	795	8.0	116	1.2	620	6.2	151	1.5	125	1.3	212	2.1	1050	10.6	1998	20.1
2020	10,016	1774	17.7	731	7.3	126	1.3	472	4.7	155	1.5	96	1.0	193	1.9	921	9.2	2054	20.5
HBV																			
2013	419	88	21.0	24	5.7	4	1.0	22	5.3	7	1.7	4	1.0	8	1.9	56	13.4	78	18.6
2017	502	102	20.3	37	7.4	4	0.8	18	3.6	19	3.8	8	1.6	5	1.0	71	14.1	63	12.5
2020	588	116	19.7	43	7.3	5	0.9	23	3.9	27	4.6	4	0.7	8	1.4	80	13.6	81	13.8
HCV																			
2013	1313	381	29.0	158	12.0	23	1.8	121	9.2	38	2.9	22	1.7	45	3.4	215	16.4	346	26.4
2017	1703	350	20.6	117	6.9	22	1.3	90	5.3	30	1.8	18	1.1	24	1.4	234	13.7	309	18.1
2020	1650	259	15.7	82	5.0	19	1.2	56	3.4	26	1.6	8	0.5	16	1.0	169	10.2	230	13.9
Alcohol																			
2013	5433	1281	23.6	551	10.1	79	1.5	491	9.0	45	0.8	75	1.4	198	3.6	570	10.5	1467	27.0
2017	4905	1192	24.3	521	10.6	74	1.5	403	8.2	68	1.4	77	1.6	145	3.0	555	11.3	1254	25.6
2020	4894	1069	21.8	478	9.8	74	1.5	327	6.7	74	1.5	56	1.1	139	2.8	483	9.9	1324	27.1

TABLE 4 | 3-year crude and age-sex-standardized overall mortality in the cohorts of subjects with chronic liver disease (CLD) enrolled in January 2013, 2017, 2020, risk ratio (RR) in the 2017 and 2020 cohorts compared to the 2013 cohort, and crude mortality by liver/non-liver causes of death.

	Crude all-cause 3-year mortality			Cause of death						Age-sex-std all-cause 3-year mortality		Age-sex std risk ratio for all-cause mortality	
				Liver diseases[a]		Other causes		Cause missing					
	n deaths	%	(95% CI)	*n* deaths	%	*n* deaths	%	*n* deaths	%	%	(95% CI)	RR[b]	(95% CI)
All CLD													
2013	3792	9.4	(9.2–9.7)	1812	4.5	1915	4.8	65	0.2	9.4	(9.1–9.7)	Ref	
2017	3276	8.3	(8.0–8.6)	1469	3.7	1760	4.5	47	0.1	8.1	(7.8–8.4)	0.86	(0.82–0.90)
2020	3363	8.2	(7.9–8.5)	1374	3.4	1922	4.7	67	0.2	8.0	(7.7–8.3)	0.85	(0.81–0.90)
HBV													
2013	176	3.1	(2.7–3.6)	76	1.4	92	1.6	8	0.1	5.0	(4.2–5.8)	Ref	
2017	208	2.9	(2.5–3.3)	80	1.1	122	1.7	6	0.1	4.4	(3.8–5.1)	0.88	(0.83–0.94)
2020	259	3.2	(2.8–3.6)	79	1.0	173	2.1	7	0.1	4.5	(3.9–5.1)	0.89	(0.84–0.95)
HCV													
2013	879	5.7	(5.3–6.0)	365	2.3	489	3.1	25	0.2	6.4	(5.9–6.8)	Ref	
2017	779	4.9	(4.6–5.3)	330	2.1	434	2.7	15	0.1	5.2	(4.8–5.6)	0.81	(0.76–0.86)
2020	744	4.7	(4.4–5.0)	231	1.5	493	3.1	20	0.1	4.9	(4.5–5.3)	0.77	(0.72–0.81)
Alcohol													
2013	1702	22.6	(21.6–23.5)	937	12.4	745	9.9	20	0.3	18.4	(17.4–19.4)	Ref	
2017	1383	23.1	(22.0–24.1)	742	12.4	628	10.5	13	0.2	18.1	(16.9–19.4)	0.99	(0.96–1.02)
2020	1439	25.0	(23.9–26.1)	763	13.2	662	11.5	14	0.2	19.8	(18.3–21.4)	1.08	(1.05–1.12)

[a]Underlying cause of death: viral hepatitis (ICD-10 codes B15-B19), liver cancer (C22), liver diseases (K70-K76), esophageal varices (I85).
[b]Estimated by means of Poisson regression models with robust error variance.

TABLE 5 | 3-year crude and age-sex-standardized overall mortality in the cohorts of subjects with cirrhosis enrolled in January 2013, 2017, and 2020, risk ratio (RR) in the 2017 and 2020 cohorts compared to the 2013 cohort, and crude mortality by liver/non-liver causes of death.

	Crude all-cause 3-year mortality			Cause of death						Age-sex-std all-cause 3-year mortality		Age-sex std risk ratio for all-cause mortality	
				Liver diseases[a]		Other causes		Cause missing					
	n deaths	%	(95% CI)	*n* deaths	%	*n* deaths	%	*n* deaths	%	%	(95% CI)	RR[b]	(95% CI)
All cirrhosis													
2013	2350	23.3	(22.5–24.1)	1466	14.5	848	8.4	36	0.4	18.7	(17.8–19.6)	Ref	
2017	1998	20.1	(19.3–20.9)	1155	11.6	819	8.2	24	0.2	16.1	(15.3–17.0)	0.86	(0.83–0.89)
2020	2054	20.5	(19.7–21.3)	1112	11.1	914	9.1	28	0.3	16.1	(15.2–17.0)	0.86	(0.83–0.89)
HBV													
2013	78	18.6	(14.9–22.3)	50	11.9	20	4.8	8	1.9	17.8	(13.4–22.3)	Ref	
2017	63	12.5	(9.7–15.4)	45	9.0	14	2.8	4	0.8	11.4	(8.3–14.5)	0.64	(0.61–0.66)
2020	81	13.8	(11.0–16.6)	51	8.7	28	4.8	2	0.3	12.8	(9.6–16.0)	0.72	(0.69–0.74)
HCV													
2013	346	26.4	(24.0–28.7)	235	17.9	102	7.8	9	0.7	22.5	(19.9–25.0)	Ref	
2017	309	18.1	(16.3–20.0)	218	12.8	88	5.2	3	0.2	16.3	(14.1–18.5)	0.73	(0.70–0.75)
2020	230	13.9	(12.3–15.6)	146	8.8	79	4.8	5	0.3	11.8	(9.9–13.6)	0.52	(0.51–0.54)
Alcohol													
2013	1467	27.0	(25.8–28.2)	907	16.7	543	10.0	17	0.3	22.3	(20.8–23.8)	Ref	
2017	1254	25.6	(24.3–26.8)	719	14.7	524	10.7	11	0.2	20.0	(18.4–21.5)	0.90	(0.87–0.92)
2020	1324	27.1	(25.8–28.3)	736	15.0	575	11.7	13	0.3	22.0	(19.9–24.1)	0.99	(0.96–1.02)

[a]Underlying cause of death: viral hepatitis (ICD-10 codes B15-B19), liver cancer (C22), liver diseases (K70-K76), esophageal varices (I85).
[b]Estimated by means of Poisson regression models with robust error variance.

FIGURE 3 | Age-sex standardized 3-year all-cause mortality (standard = all subjects with chronic liver disease in 2013) with 95% confidence intervals for the cohorts enrolled in January 2013, 2017, and 2020. All patients and patients with cirrhosis.

approach might be to investigate subjects with both CLD and selected metabolic conditions (e.g. diabetes, obesity). Thirdly, we could not distinguish between compensated and decompensated cirrhosis [26], which are two distinct stages with different healthcare associated burden [29] and risks of mortality [7]. However, it is likely that most liver-related deaths among patients with cirrhosis occurred in those with decompensated disease; therefore, the overall analysis of mortality risk associated with cirrhosis should not be significantly affected by this limitation. Fourth, potential biases remain due to the exclusion of certain treatments, such as TIPS placement or anticancer therapies. Finally, these regionally based data are not necessarily fully representative of the Italian scenario. However, major epidemiological and clinical trends, including the impact of immigration on HBV-related CLD, the peak in HCV-related CLD among the 1960s birth cohort, and the progressive introduction of DAAs, starting from December 2014, limited to patients with severe liver disease and subsequently expanded to include all HCV patients by 2017, are all common features at the national level [14, 18]. We therefore believe that our study could be useful to plan additional actions and interventions in the Veneto region, stimulating further studies to better assess the current epidemiology of CLD in similar settings.

In conclusion, the study depicts a changing scenario of CLD and cirrhosis in Northeastern Italy. Over the last decade, while the overall prevalence of CLD remained stable, significant shifts were observed for specific aetiologies. The introduction of direct-acting antivirals has markedly improved outcomes for HCV-related CLD. In contrast, the persistently high mortality associated with alcohol-related CLD, especially during the pandemic, highlights the need for targeted and multidisciplinary interventions. Future efforts should focus on expanding access to care for high-risk populations, including immigrants with HBV. These insights can inform policies aimed at mitigating the morbidity and mortality burden associated with CLD and cirrhosis.

Author Contributions

F.P.R.: data collection and analysis, interpretation of study results, writing, revision, and final approval of the manuscript. A.Z.: interpretation of study results, writing and revision of the manuscript. L.S.: data collection and analysis, interpretation of study results, writing and revision of the manuscript. C.B.A.: interpretation of study results, writing and revision of the manuscript. S.B., S.P., P.A., and P.B.: revision of the manuscript. M.S.: data collection and analysis, interpretation of study results, writing and revision of the manuscript. U.F.: data collection and analysis, interpretation of study results, writing and revision of the manuscript. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data not available due to ethical/legal restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.