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Mortality Attributable to Hepatitis B and C in Italy, Romania, and Spain, 2022 Estimates

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Abbreviations: AFs, Attributable fractions; DAAs, Direct-acting antivirals; ECDC, The European Centre for Disease Prevention and Control; European Economic Area, EEA; European Union, EU; GBD, Global Burden of Disease; GHSS, Global Health Sector Strategy; HBsAg, Hepatitis B surface antigen; HBV, Hepatitis B virus; HCC, Hepatocellular carcinoma; HCV, Hepatitis C virus; HDV, Hepatitis D virus; ICD-10, International Classification of Diseases, 10th Revision; Research Electronic Data Capture, REDCap; RR, Relative risk; WHO, World Health Organisation.

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ABSTRACT

Background and Aims: Reliable data on viral hepatitis–related deaths remain limited, challenging assessment of progress towards the WHO elimination targets for mortality. To address this gap, we estimated hepatitis B- and C-attributable mortality in Italy, Romania, and Spain for 2022.

Methods: Retrospective hospital data on decompensated cirrhosis and hepatocellular carcinoma cases were collected from sentinel sites in each of three countries using standard WHO protocol. The data were used to calculate fractions of these diseases attributable to hepatitis B and C. Adjusted and weighted attributable fractions were applied to national vital statistics data on deaths from cirrhosis and hepatocellular carcinoma from Eurostat to produce national hepatitis mortality estimates.

Results: A total of 1733 cases of decompensated cirrhosis and hepatocellular carcinoma cases were enrolled into the study from sentinel sites across Italy, Romania, and Spain. We estimated that the share of decompensated cirrhosis deaths attributed to hepatitis B was: 8.7% in Italy, 16.8% in Romania and 1.8% in Spain. The respective share of hepatocellular carcinoma deaths attributed to hepatitis B was 19.0% in Italy, 31.2% in Romania and 4.9% in Spain. Hepatitis C accounted for 61.6% of hepatocellular carcinoma deaths in Italy, 36.5% in Romania, and 31.1% in Spain, as well as 32.9% of decompensated cirrhosis deaths in Italy, 18.8% in Romania and 12.7% in Spain. Overall, hepatitis B-related mortality per 100 000 population was 3.1 in Italy, 12.0 in Romania and 0.6 in Spain. Hepatitis C-related mortality was 11.4 per 100 000 population in Italy, 13.8 in Romania and 3.7 in Spain.

Conclusions: Our study yielded empirical data needed to estimate hepatitis mortality for assessing the impact of hepatitis strategies. Whilst our results indicate a reduction in deaths related to hepatitis B and C in Italy and Spain, none of the three countries was meeting the WHO's 2025 target for hepatitis C-related mortality, although the hepatitis B-related mortality target was met by Italy and Spain. Our findings highlight the need for countries to continue strengthening efforts to prevent and control viral hepatitis and to integrate such assessments into national surveillance to guide effective targeting of interventions and monitoring of progress towards the elimination targets.

Key Points

- Reducing hepatitis-related mortality is a key indicator for achieving hepatitis B and C elimination by 2030.
- Estimation of mortality is challenging but can be derived by applying aetiological fractions of hepatitis B and C to deaths from decompensated cirrhosis and hepatocellular carcinoma.
- In 2022, hepatitis B mortality per 100 000 population was 3.1 in Italy, 12.0 in Romania and 0.6 in Spain; hepatitis C mortality was 11.4, 13.8 and 3.7, respectively.
- None of the countries met the WHO 2025 target for hepatitis C mortality (≤3/100000), while Italy and Spain met the hepatitis B target (≤7/100000).

1 | Introduction

In 2016, the World Health Organisation (WHO) launched the Global Health Sector Strategy (GHSS) on viral hepatitis, setting an ambitious goal to eliminate hepatitis B and C as public health threats by 2030 [1]. A key criterion for elimination, as defined by the GHSS, is a 65% reduction in mortality attributable to hepatitis B virus (HBV) and hepatitis C virus (HCV) infections by 2030 from the 2015 baseline. The updated GHSS for 2022–2030, along with WHO guidance for country-level validation, emphasises the use of an absolute impact target, specifically, reducing HBV- and HCV-related combined mortality to below 6 deaths per 100 000 population respectively by 2030, rather than relying solely on relative reductions from baseline levels. The WHO interim 2025 targets for hepatitis-related mortality in Europe were set at ≤7 deaths per 100 000 population for HBV and ≤3 deaths per 100 000 population for HCV [2, 3].

Accurate national mortality estimates for viral hepatitis are essential for monitoring progress towards the elimination targets and for guiding public health responses. However, most countries lack robust data to estimate liver disease mortality related to chronic HBV and HCV infections. Indeed, the reporting of hepatitis related deaths due to these sequelae (primarily decompensated cirrhosis and hepatocellular carcinoma (HCC)) through vital statistics has significant flaws due to limitations in death certification practices, which often result in the omission of the underlying aetiology [4–6]. The European Centre for Disease Prevention and Control (ECDC) previously undertook a study to estimate HBV and HCV attributable mortality in European Union (EU) and European Economic Area (EEA) countries in 2015 by adjusting vital statistics mortality data on HCC and chronic liver disease using attributable (aetiological) fractions (AFs) for chronic HBV and HCV [7]. Because country-specific AFs estimates were lacking, the analysis applied modelled estimates from Global Burden of Disease (GBD) publications and the published literature acknowledging that these inputs were based on sparse and, in places, outdated data [7].

To address the gap in national mortality estimates, WHO developed a standardised protocol to support countries in generating national mortality estimates for HBV and HCV [8, 9]. The protocol outlines a three-step approach: (i) estimating the proportion of decompensated cirrhosis and HCC cases attributable to HBV and HCV (AFs); (ii) quantifying total deaths from chronic liver disease using national vital statistics data; and (iii) applying AFs to the vital statistics data to calculate HBV- and HCV-related mortality rates per 100 000 population.

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Lay Summary

This study aimed to estimate how many people in Italy, Romania, and Spain died from liver diseases caused by hepatitis B and hepatitis C. By analysing hospital records and national statistics data, researchers estimated the contribution of these viruses to deaths from cirrhosis and hepatocellular carcinoma. In 2022, all three countries failed to meet the WHO's 2025 interim target for hepatitis C-related mortality of no more than 3 deaths per 100 000 people; however, Italy and Spain met the target for hepatitis B of no more than 7 deaths per 100 000. These findings highlight the need for countries to continue strengthening efforts to prevent and control viral hepatitis.

A pilot study based on an earlier version of the WHO protocol was conducted by the ECDC in Bulgaria, Norway, and Portugal in 2016 [10]. The pilot highlighted several practical challenges in implementing the protocol, such as the significant time and human resources required to collect data and underscored the value of focusing on decompensated cirrhosis cases to achieve more accurate aetiological attribution. Building on these insights, ECDC initiated a new project to support EU/EEA Member States in developing mortality estimates using empirical data.

Three countries of the EU/EEA agreed to join the project and allocated the necessary resources to implement the study protocol and collect data: Italy, Romania and Spain.

Historically, Italy reported some of the highest prevalence rates of HCV in Europe, largely driven by a pronounced cohort effect among older birth-cohorts exposed via iatrogenic routes, with anti-HCV prevalence reaching up to 33.1% among individuals aged over 60 years in a survey conducted in Southern Italy [11, 12]. Over time, prevalence has declined due to mortality among the infected cohort and the impact of curative measures, further supported by universal access to direct-acting antivirals (DAAs) in Italy since 2017, with active HCV infection estimated at 0.7% in 2022 [13]. HBV prevalence in the country is lower, largely due to the early introduction of universal childhood HBV vaccination, with the most recent estimates from 2025 indicating that 0.2% of the population lives with chronic infection [14].

In Romania, the prevalence of HCV was also among the highest in the region with an estimated prevalence of 3.2% from a survey conducted in 2006–2008, but prevalence has also fallen dramatically due to the impact of large-scale treatment and mortality with the most recent national survey conducted in 2020 reporting a 0.9% prevalence of chronic HCV [15, 16]. The prevalence of HBV in Romania remains one of the highest in the region with the national prevalence survey in 2020 finding an HBV prevalence of 6.2% among the general populations [17].

Finally, in Spain, the estimated prevalence of HCV antibodies in the general population was 0.9% and the prevalence of active HCV infection was 0.2% in 2017–2018 [18]. Recent estimates from modelling studies have shown a decreasing trend in active HCV prevalence in the general population: 0.2% in 2019 [19] and 0.1% in 2022 [20] reflecting the large number of people treated with DAAs [21]. Regarding HBV, the prevalence of active HBV infection found in a seroprevalence study in the general population in 2017–2018 was low, with an overall rate of hepatitis B surface antigen (HBsAg) carriers of 0.2% and viremic carriers of less than 0.1% [22].

The aim of this project was to estimate national mortality attributable to HBV and HCV for Italy, Romania, and Spain following the WHO protocol for 2022 [4, 9]. To achieve this aim, the study pursued the following objectives:

1. Estimate the aetiological fractions (also referred to as crude AFs) of decompensated cirrhosis and HCC due to HBV and HCV.
2. Quantify the total deaths (mortality envelopes) from cirrhosis and HCC, as well as direct deaths from HBV, and HCV reported in each country.
3. Weight crude AFs according to the sex and age distribution of mortality envelopes
4. Adjust weighted AFs based on the relative risk (RR) of sequelae development in individuals with HBV and HCV.
5. Apply the adjusted weighted AFs to mortality data to produce national estimates of HBV- and HCV-related mortality.

2 | Methods

2.1 | Study Centres and Population

To estimate the aetiological fractions, study centres in each of the three participating countries were selected using the following stepwise approach:

1. All centres in the country that manage patients with both decompensated cirrhosis and HCC were identified.
2. Centres that primarily serve specific population or populations with a higher prevalence of HCV and HBV were excluded (e.g., focus solely on people who inject drugs).
3. Centres treating fewer than 100 patients with decompensated cirrhosis or HCC annually were excluded.
4. From the remaining centres, one site in the capital (or another major city) and two to eight sites in other regions were selected to ensure a balanced representation of patients with decompensated cirrhosis and HCC to reflect geographical and epidemiological differences.

National public institutes invited selected centres to participate in the study. Participation of the centres was voluntary. In the event of the centre's refusal, an alternative centre that met the requirements was invited. A list of participating centres is available in Appendix.

2.2 | Sample Size Calculation

The sample size for the estimates was calculated to obtain a 95% confidence interval for the proportion of patients with

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BOX 1 | Formula for sample size calculations.

$$n = \frac{Z^2 P(1-P)}{d^2} - 10\%$$

where, n = required sample size; Z = Z-score for 95% confidence level (1.96); P = expected prevalence; d = desired precision level.

decompensated cirrhosis or HCC (analysed separately) who had HCV and/or HBV. The formula [23] in Box 1 was used separately for decompensated cirrhosis and for HCC.

In calculating the sample size, the expected prevalence for HCV and HBV among patients with decompensated cirrhosis in each country was derived from the GBD study [7, 24]. Since HCV was more prevalent than HBV among patients with decompensated cirrhosis and HCC in all countries, the estimated prevalence was used for sample size calculation, as larger sample sizes are required when the underlying prevalence approaches 50%. An absolute precision of 5% was applied. The formula also accounted for an assumed average 10% incidence of HCC among patients with cirrhosis [25].

According to GBD estimates, in Italy in 2015, 55% of cirrhosis cases and 63% of HCC cases were attributed to HCV, resulting in a sample size of 342 for decompensated cirrhosis and 322 for HCC. In Romania, HCV accounted for approximately 24% of cirrhosis and 25% of HCC cases, resulting in a sample size of 252 decompensated cirrhosis cases and 259 HCC cases. Finally, in Spain, HCV was estimated to be the cause of 28% of cirrhosis cases and 62% of HCC cases, resulting in a sample size of 279 cases for decompensated cirrhosis and 326 for HCC. The total sample was proportionally distributed across participating centres based on the annual number of relevant patients seen at each site.

2.3 | Data Sources and Collection

Data collection consisted of two components. The first component involved a retrospective data collection from hospital registers of data needed to estimate AFs for patients identified to have decompensated cirrhosis and HCC. The second component consisted of a desk review of mortality data on cirrhosis and HCC obtained from Eurostat to calculate mortality envelopes.

2.3.1 | Component 1. Aetiological Fraction Estimates

For the first component, eligible cases were identified using specific International Classification of Diseases, 10th Revision (ICD-10) codes, which were selected based on the clinical definition of decompensated cirrhosis as a case exhibiting clinical symptoms of acute or non-acute decompensation (acute decompensation: first or recurrent grade 2 or 3 ascites within less than 2 weeks, first or recurrent acute hepatic encephalopathy in patients with previous normal consciousness, acute gastrointestinal bleeding, and any type of acute bacterial infection; non-acute decompensation: slow ascites formation, mild grade 1 or 2 hepatic encephalopathy, or progressive jaundice in non-cholestatic cirrhosis [26]).

The following algorithm for selecting eligible patient records in electronic patient registers was applied by hospital staff in selected centres.

2.3.2 | Step 1: Search was Done Using ICD-10 Code K70-K77 (An Overarching Term for All Patients With Advanced Liver Disease), Including

- K70 Alcoholic liver disease,
- K71 Toxic liver disease with cholestasis,
- K72 Liver failure,
- K73 Chronic hepatitis,
- K74 Fibrosis and cirrhosis of the liver,
- K75 Other inflammatory liver diseases,
- K76 Other diseases of the liver,
- K77 Liver disorders in infectious and parasitic diseases classified elsewhere.

2.3.3 | Step 2: Filtering was Performed for Manifestations of Decompensated Liver Cirrhosis Using the Following ICD-10 Codes

- R18 Ascites,
- I85.0 Oesophageal varices with bleeding,
- K76.7 Hepatorenal syndrome,
- K72.7 Hepatic encephalopathy.

Cases of HCC, which is clinically defined as a primary malignancy of hepatocytes confirmed by imaging or pathology [27], were identified using codes C22.0 and C22.9.

The data was collected by coordinators delegated by the participating centre in accordance with the following algorithm:.

1. Patient databases were reviewed consecutively from the beginning of 2023. For each case with decompensated cirrhosis or HCC as defined by ICD-10 codes, investigators made an entry in the logbook. If the case was unique (no duplication), the case was enrolled in the study and assigned an individual study number. Patients with both HCC and decompensated cirrhosis were assigned to the HCC cohort, as HCC is commonly associated with cirrhosis, which represents a major risk factor for its development and is linked to more severe health outcomes [28].
2. The data for each case (Appendix S2) was then extracted and entered by a coordinator at each hospital into the

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Research Electronic Data Capture (REDCap) database with data stored on the ECDC server. Data extracted included age, sex, diagnostic testing showing HBV or HCV infection, excessive alcohol consumption (as per local definition), and metabolic syndrome components (diabetes, obesity – as per local definition).

The following definitions were used to determine whether a person had HBV or HCV infection:

- Chronic HBV infection: Ever testing positive for HBsAg or HBV DNA.
- HCV infection (past or chronic): Ever testing positive for anti-HCV, HCV RNA, or HCV antigen test.

2.3.4 | Component 2. Mortality Envelopes

For the second component, mortality data for advanced liver diseases by 5-year age group and sex for each of the three countries were obtained from Eurostat using the following primary codes: K70, K72, K73, K74, K76.0, I85.0 for cirrhosis, and C22.0, C22.9 for HCC. Additionally, data on direct mortality from hepatitis as a primary cause of death were also obtained across the following codes: HBV—B16.0, B16.2, B16.9, B18.0, B18.1; HCV—B17.1, B18.2 (see Table 3).

Population size estimates for the participating countries were also obtained from Eurostat [29].

2.4 | Data Collection Period

Data for the first component were collected in Romania between November 2024 and January 2025, in Italy between February 2025 and June 2025, and in Spain between March 2025 and September 2025. Data collection was retrospective, covering patients admitted from 1 January 2023 until the sample size was reached, but no later than 31 December 2023. The most recent mortality data available from Eurostat were from 1 January 2022 to 31 December 2022. Corresponding population size estimates were obtained from Eurostat as of 1 January 2022.

2.5 | Data Analysis to Develop Adjusted AFs Estimates

2.5.1 | Step 1: Estimate Crude AFs of Decompensated Cirrhosis and HCC due to HBV and HCV

Data collected from the study sites were cleaned and screened for implausible values. Two outcomes were analysed: HCC (regardless of cirrhosis status) and decompensated cirrhosis without known HCC. Crude AFs were calculated as the proportion of patients with HBV or HCV among those with each outcome. For cases that had both HBV and anti-HCV positivity but negative HCV RNA/HCV antigen, their sequelae were attributed to HBV in crude analysis.

2.5.2 | Step 2: Quantify the Total Deaths (Mortality Envelopes) From Cirrhosis and HCC, as Well as Direct Deaths From HBV and HCV Reported in Each Country

Data from Eurostat for the second component were summarised to produce total count (mortality envelopes) of people whose primary reason of deaths was: (a) decompensated cirrhosis; (b) HCC; (c) direct mortality from HCV as the primary cause; and (d) direct mortality from HBV as the primary cause.

2.5.3 | Step 3: Weight Crude AFs According to the Sex and Age Distribution of Mortality Envelopes

For each outcome (HCC and decompensated cirrhosis without HCC), mortality counts from Eurostat were stratified by sex and 5-year age groups. These counts were matched with the empirical crude AF data from the countries. Crude AFs for mortality were recalculated by weighting the initial crude AF estimates by age and sex groups using their respective ratios between two data sources.

2.5.4 | Step 4: Adjust Weighted AFs Based on the RR of Sequelae Development in Individuals With HBV and HCV

The crude weighted estimates were further adjusted using formula in Box 2 [10] to account for instances when individuals had the risk factor (e.g., HBH or HCV infection) but would have developed advanced liver disease regardless of it. The RR of developing advanced liver diseases for patients with HBV and HCV was derived from the literature (RR for HCV was 51.1 and for HBV 20.4.) [1, 30–33].

2.5.5 | Step 5: Apply the Adjusted Weighted AFs to Mortality Data to Produce National Estimates of HBV- and HCV-Related Mortality

The adjusted weighted AFs were applied to the mortality envelopes in order to produce HBV and HCV mortality estimates using the formula presented in Box 3.

Mortality estimates were expressed per 100 000 population by dividing the total number of deaths attributable to HBV and HCV by the size of population and multiplying by 100 000.

3 | Ethics

The approval for the project was obtained in each participating country: in Italy—by the National Ethical Committee

BOX 2 | Formula for adjusted analysis [10].

$$\text{AdjustedAF} = \frac{\text{CrudeAF} * (\text{RR} - 1)}{\text{RR}}.$$

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BOX 3 | Formulas for mortality estimates [9].

- **Deaths attributable to HBV** = (adjusted weighted AF of HBV infection × Number of deaths from HCC in the specified year) + (% of people with decompensated cirrhosis with HBV infection × Number of deaths from cirrhosis and decompensated cirrhosis in the specified year) + Number of direct deaths from HBV as primary cause in the specified year.
- **Deaths attributable to HCV** = (adjusted weighted AF of HCV infection (current or past) × Number of deaths from HCC in the specified year) + (% of people with decompensated cirrhosis with HCV infection (current or past) × Number of deaths from decompensated cirrhosis in the specified year) + Number of direct deaths from HCV as primary cause in the specified year.

of the Istituto Superiore di Sanità (approval no. 0054445, 23 December 2024), in Romania—from the Scientific Council and the Ethical Committee of the National Institute of Public Health (approval no. 17544/07.10.2024 and from each participating hospital), in Spain—from Comité De Ética De Investigación Con Medicamentos Del Hospital Universitari Vall D'hebron (approval PR(AG)530/2024) and additionally from each participating hospital (Servizo Galego de Saúde and Comité de Ética de la Investigación con Medicamentos del Hospital Gregorio Marañón).

The data collected from sentinel sites was pseudonymised case-based data extracted from hospital registers and/or case notes. In order to ensure fully confidentiality, only assigned individual study numbers (not linked directly with the patient) were used in the data collection forms and REDCap database, ensuring that only anonymised patient data were collected into the database. The data collected at each of the sites were transferred electronically to ECDC via the REDCap platform and were stored securely on the ECDC servers.

4 | Results

4.1 | Study Population

To estimate fractions of liver diseases sequelae attributable to HBV and HCV, a total of 1733 cases were enrolled across Italy, Romania, and Spain, comprising both decompensated cirrhosis and HCC patients. As presented in Table 1, Italy contributed 485 cases, with 198 (40.8%) diagnosed with decompensated cirrhosis without known HCC and 287 (59.2%) with HCC. Romania reported 855 cases, including 500 (58.5%) cases with decompensated cirrhosis and 355 (41.5%) cases with HCC. Spain included 393 cases: 205 (52.2%) cases with decompensated cirrhosis and 188 (47.8%) with HCC. In each country, the majority of cases were male both among decompensated cirrhosis and HCC cases. Mean ages for decompensated cirrhosis ranged from 57.8 years in Romania to 61.4 years in Italy, while for HCC, they ranged from 65.0 years in Romania to 68.2 years in Italy.

4.2 | Crude AFs

In crude analysis, in 2023 the contributions of HBV and HCV to decompensated cirrhosis and HCC varied across countries. In Italy, HBV accounted for 11.6% (95% CI: 7.7–17.1) and HCV for 23.7% (18.1–30.4) of decompensated cirrhosis cases, while 23.7% (19.0–29.1) and 59.2% (53.3–64.9) of HCC cases were attributed to HBV and HCV, respectively. In Romania, HBV contributed to 19.6% and HCV to 18.6% of decompensated cirrhosis cases, and 33.0% and 37.7% of HCC cases, respectively. In Spain, HBV accounted for 2.4% (95% CI: 0.9–5.9) and HCV for 14.6% (10.2–20.4) of decompensated cirrhosis cases, while 6.9% (3.9–11.8) and 33.0% (26.4–40.3) of HCC cases were attributed to HBV and HCV, respectively (Table 2).

4.3 | Mortality Envelopes

According to Eurostat data from 2022, liver-related mortality varied across Italy, Romania, and Spain. In Italy, there were 5451 deaths from cirrhosis and 6166 from HCC, with an additional 202 deaths listing HBV and 1140 listing HCV as the primary cause (Table 3). In Romania, 9308 deaths were recorded from cirrhosis and 2245 from HCC, with an additional 21 deaths directly attributed to HBV and 57 to HCV as the primary cause. In Spain, there were 4498 deaths from cirrhosis and 3061 from HCC, with 52 deaths directly listing HBV and 225 directly listing HCV as the primary cause (Table 3).

4.4 | Adjusted Weighted AFs

After weighting AFs by the age and sex structure of cirrhosis and HCC mortality data for 2022 obtained from Eurostat and performing adjustment, the AFs slightly decreased. In Italy, HBV accounted for 8.7% (95% CI: 5.4–13.0) and HCV for 32.9% (26.8–39.4) of decompensated cirrhosis cases, while 19.0% (14.9–23.6) and 61.6% (56.1–66.8) of HCC cases were attributed to HBV and HCV, respectively. In Romania, HBV contributed to 16.8% (13.8–20.1) and HCV to 18.8% (15.6–22.2) of decompensated cirrhosis cases, and 31.2% (26.6–35.9) and 36.5% (31.7–41.4) of HCC cases, respectively. In Spain, HBV accounted for 1.8% (0.6–4.2) of decompensated cirrhosis cases and 4.9% (2.5–8.5) of HCC cases, while HCV contributed to a substantially higher proportion: 12.7% (8.7–17.6) of decompensated cirrhosis cases and 31.1% (24.9–37.7) of HCC cases.

4.5 | Mortality Estimates

After applying adjusted, weighted AFs to mortality envelopes and incorporating deaths where hepatitis was the underlying cause, in Italy an estimated 1848 deaths (95% CI: 1509–2187) were attributable to HBV and 6731 deaths (6255–7207) to HCV, corresponding to mortality rates of 3.1 (2.6–3.7) and 11.4 (10.6–12.2) per 100 000 population, respectively (Table 4). In Romania in turn, 2283 deaths (1941–2625) were attributable to HBV and 2623 deaths (2219–3207) to HCV, corresponding to mortality rates of 12.0 (10.2–13.8) for HBV and 13.8 (11.7–15.9) for HCV. Finally, in Spain an estimated 283 deaths (161–405) were

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TABLE 1 | Clinical and demographic characteristics of incident cases of decompensated cirrhosis and HCC in Italy, Romania and Spain, 2023.

	Italy		Romania		Spain	
Characteristic	**Decompensated cirrhosis, *n* (%)**	**HCC, *n* (%)**	**Decompensated cirrhosis, *n* (%)**	**HCC, *n* (%)**	**Decompensated cirrhosis, *n* (%)**	**HCC, *n* (%)**
Total	198 (100)	287 (100)	500 (100)	355 (100)	205 (100)	188 (100)
Sex						
Male	137 (69.2)	230 (80.1)	319 (63.8)	249 (70.1)	153 (74.6)	153 (81.4)
Female	60 (30.3)	57 (19.9)	177 (35.4)	106 (29.9)	52 (25.4)	35 (18.6)
Unknown	1 (0.5)	0 (0)	4 (0.8)	0 (0)	0 (0)	0 (0)
Mean age	61.4	68.2	57.8	65.0	61.3	66.5
Admission						
Inpatient	79 (39.9)	93 (32.4)	442 (88.4)	341 (96.1)	143 (69.8)	43 (22.9)
Outpatient	119 (60.1)	194 (67.6)	56 (11.2)	13 (3.7)	61 (29.8)	145 (77.1)
Unknown	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.3)	1 (0.5)	0 (0)
Viral markers						
HBsAg						
Yes	21 (10.6)	67 (23.3)	97 (19.4)	117 (33.0)	5 (2.4)	13 (6.9)
No	155 (78.3)	195 (67.9)	400 (80.0)	234 (65.9)	200 (97.6)	174 (92.6)
Unknown	22 (11.1)	25 (8.7)	3 (0.6)	4 (1.1)	0 (0)	1 (0.5)
HBV DNA						
Yes	7 (3.5)	17 (5.9)	59 (11.8)	38 (10.7)	0 (0)	5 (2.6)
No	82 (41.4)	179 (62.4)	275 (55.0)	243 (68.5)	128 (62.8)	91 (48.4)
Unknown	109 (55.1)	91 (31.7)	166 (33.2)	74 (20.8)	77 (37.2)	92 (48.9)
Anti-HCV						
Yes	49 (24.7)	171 (59.6)	95 (19.0)	137 (38.6)	30 (14.6)	63 (33.5)
No	133 (67.2)	106 (36.9)	401 (80.2)	216 (60.8)	175 (85.4)	124 (65.9)
Unknown	16 (8.1)	10 (3.5)	4 (0.8)	2 (0.6)	0 (0)	1 (0.6)
HCV RNA						
Yes	11 (5.6)	26 (9.1)	13 (2.6)	32 (9.0)	2 (1.0)	5 (2.6)
No	84 (42.4)	197 (68.6)	419 (83.8)	289 (81.4)	130 (63.4)	114 (60.6)
Unknown	103 (52.0)	64 (22.3)	68 (13.6)	34 (9.6)	73 (35.6)	69 (36.7)
HCV-antigen						
Yes	0 (0)	1 (0.3)	0 (0)	0 (0)	2 (1.0)	3 (1.6)
No	14 (7.1)	37 (12.9)	13 (2.6)	11 (3.1)	132 (64.7)	115 (61.2)
Unknown	284 (92.9)	249 (86.8)	487 (97.4)	344 (96.9)	71 (34.3)	70 (37.2)
Co-morbidities						
Obesity						
Yes	52 (26.3)	42 (14.6)	55 (11.0)	35 (9.9)	52 (25.4)	49 (26.1)
No	145 (73.2)	240 (83.6)	440 (88.0)	0 (0.0)	147 (71.7)	130 (69.1)
Unknown	1 (0.5)	5 (1.7)	5 (1.0)	0 (0.0)	6 (2.9)	9 (4.8)

(Continues)

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TABLE 1 | (Continued)

Characteristic	Italy		Romania		Spain	
	Decompensated cirrhosis, *n* (%)	HCC, *n* (%)	Decompensated cirrhosis, *n* (%)	HCC, *n* (%)	Decompensated cirrhosis, *n* (%)	HCC, *n* (%)
Diabetes						
Yes	66 (33.3)	77 (26.8)	90 (18.0)	76 (21.4)	70 (34.1)	70 (37.2)
No	131 (66.2)	204 (71.1)	405 (81.0)	276 (77.7)	133 (64.8)	116 (61.7)
Unknown	1 (0.5)	6 (2.1)	5 (1.0)	3 (0.8)	2 (1.0)	2 (1.1)
MASLD						
Yes	68 (34.3)	42 (14.6)	10 (2.0)	16 (4.5)	67 (35.6)	57 (30.3)
No	128 (64.6)	207 (72.1)	486 (97.2)	330 (93.0)	135 (73.4)	128 (68.1)
Unknown	2 (1.0)	6 (2.1)	4 (0.8)	9 (2.5)	3 (1.5)	3 (1.6)
Excessive alcohol consumption						
Yes	107 (54.0)	82 (28.6)	330 (66.0)	125 (35.2)	132 (64.4)	95 (50.5)
No	88 (44.4)	202 (70.4)	166 (33.2)	223 (62.8)	73 (35.6)	92 (48.9)
Unknown	3 (1.5)	3 (1.0)	4 (0.8)	7 (2.0)	0	1 (0.6)
Other liver diseases (e.g., Wilson's diseases, haemochromatosis, auto-immune hepatitis etc.)						
Yes	40 (20.2)	74 (25.8)	27 (5.4)	2 (0.6)	25 (12.2)	9 (4.8)
No	154 (77.8)	151 (52.6)	468 (93.6)	350 (98.6)	179 (95.2)	176 (93.6)
Unknown	4 (2.0)	3 (1.0)	5 (1.0)	3 (0.8)	1 (0.5)	3 (1.6)

Abbreviations: Anti-HCV, hepatitis C virus antibody; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; HCC, hepatocellular carcinoma; HCV RNA, hepatitis C virus ribonucleic acid; HCV-antigen, hepatitis C virus core antigen; MASLD, metabolic dysfunction associated steatotic liver disease.

attributable to HBV and 1748 deaths (1468–2028) to HCV, corresponding to mortality rates of 0.6 (0.3–0.9) and 3.7 (3.1–4.3) per 100 000 population, respectively.

5 | Discussion

This study presents the first up-to-date empirical estimation of hepatitis-attributable mortality in Italy, Romania, and Spain using the WHO standardised protocol. Our study collected empirical data on cases of decompensated cirrhosis and HCC across Italy, Romania, and Spain and revealed distinct patterns in the aetiology and clinical characteristics of these cases. In all three countries, HCC patients, as expected, were generally older and more likely to be male compared to those with decompensated cirrhosis. When comparing the fractions of HCV and HBV in cases of decompensated cirrhosis and HCC, Italy showed a predominance of HCV, particularly in HCC, whereas Romania showed similar contributions of HBV and HCV across both conditions. Spain had a lower fraction compared to Italy and Spain, but with HCV still being a major contributor to HCC and HBV having a relatively minor role for both decompensated cirrhosis and HCC. Adjusted weighted AFs aligned with mortality data showed a slight decrease compared to crude estimates, mostly related to the older age of patients who died from decompensated cirrhosis and HCC, compared to those newly diagnosed and admitted to care. However, the adjusted weighted AFs remained consistent with the patterns observed in the crude estimates.

When comparing our data with modelled estimates from the 2015 ECDC analysis [7], which applied GBD-derived AFs that were based on a literature review and modelling, we observed a notable decrease in the HCV AFs among patients with decompensated cirrhosis across all countries studied and a decrease in HCC AFs in Spain. This decrease is accompanied by a simultaneous increase in the AFs for HBV for both conditions in Romania and for HCC in Italy. These changes around the HCV AFs may be attributed to the successful scale-up of DAA treatment for HCV, which began in Spain in 2014 [30], followed by Italy, with access for patients with advanced liver disease in 2015 and expanded to universal access in 2017 [31], and in Romania with initial access for patients with cirrhosis in 2015–2016, followed by broader inclusion in 2017 [34]. The role of DAAs in the significant reduction of hospitalisation rates for HCC and decompensation cirrhosis cases has been recently documented [35]. We also acknowledge that the methodology in the original GBD study used modelled AFs, rather than empirical data and the AFs of HBV for HCC in Italy and of HCV for HCC in Romania may have been underestimated and should be compared with the results from the present study with a caution due to these methodological differences. This underscores the importance of using up-to-date, country-specific data to inform national hepatitis

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TABLE 2 | Estimated aetiological fractions of decompensated cirrhosis and HCC attributed to HBV and HCV in Italy, Romania and Spain, 2023.

Country	Condition	Type of hepatitis	Attributable fractions			
			Crude, % (95% CI)	Weighted crude*, % (95% CI)	Adjusted weighted**, % (95% CI)	GBD[a], (2015), %
Italy	Decompensated cirrhosis	HBV	11.6 (7.7–17.1)	9.2 (5.7–13.7)	8.7 (5.4–13.0)	14.9
		HCV	23.7 (18.1–30.4)	34.2 (27.8–40.9)	32.9 (26.8–39.4)	54.6
	HCC	HBV	23.7 (19.0–29.1)	20.0 (15.6–24.8)	19.0 (14.9–23.6)	8.0[b]
		HCV	59.2 (53.3–64.9)	63.9 (58.2–69.3)	61.6 (56.1–66.8)	63.0
Romania	Decompensated cirrhosis	HBV	19.6 (16.3–23.4)	17.7 (14.5–21.2)	16.8 (13.8–20.1)	16.4
		HCV	18.6 (15.3–22.4)	19.5 (16.2–23.1)	18.8 (15.6–22.2)	23.7
	HCC	HBV	33.0 (28.1–38.1)	32.8 (28.0–37.8)	31.2 (26.6–35.9)	13.0
		HCV	37.7 (32.7–43.0)	37.9 (32.9–43.0)	36.5 (31.7–41.4)	25.0
Spain	Decompensated cirrhosis	HBV	2.44 (0.9–5.91)	1.9 (0.6–4.4)	1.8 (0.6–4.2)	9.4
		HCV	14.6 (10.2–20.4)	13.2 (9.0–18.3)	12.7 (8.7–17.6)	27.6
	HCC	HBV	6.9 (3.9–11.8)	5.2 (2.6–9.0)	4.9 (2.5–8.5)	10.0
		HCV	33.0 (26.4–40.3)	32.2 (25.8–39.1)	31.1 (24.9–37.7)	62.0

Abbreviations: GBD, Global Burden of Disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.
[a]GBD estimates are for 'Malignant neoplasm of liver and intrahepatic bile duct' (ICD-10 C22) and for 'Cirrhosis and other chronic liver diseases' (B18-B18.9, I85-I85.9, I98.2, K70-K70.3, K71.7, K74-K74.9, K75.2, K75.4-K76.2, K76.4-K76.9, K77.8). Source: GBD Results Tool cause-specific mortality estimates for deaths, http://ghdx.healthdata.org/gbd-results-tool. The estimates published by GBD are outputs of Bayesian meta-regression tool DisMod-MR 2.1. (more details about GBD's subclause proportions model at 10.1016/S0140–6736(17)32152-9).
[b]All values in the table were standardised to one decimal place. For GBD fractions for HCC, a trailing '0.0' was added where the original data had no decimal.
*Weighted attributable fractions account for the difference in age and sex structure between incident decompensated cirrhosis HCC cases and mortality from the two diseases.
**Adjustment accounts for instances when individuals had the risk factor (e.g., HBV or HCV infection) but would have developed advanced liver disease regardless of it.

strategies, as global estimates may not fully capture local epidemiological dynamics. In the pilot study [10] differences were also found in the AFs for HCC and cirrhosis compared to the GBD estimates, and these differences for cirrhosis may be due to the pilot study not distinguishing the decompensation status of cirrhosis patients.

In relation to mortality estimates based on Eurostat data for 2022, all three countries were falling short of the WHO 2025 interim impact targets for the European region for HCV, which is defined as ≤3 deaths per 100 000 population [3], although Spain appeared closest to reaching the threshold. By contrast, the estimates indicated that Italy and Spain were within the WHO 2025 interim target for HBV-related mortality (≤7 deaths per 100 000 population), whereas Romania exceeded this level. Nevertheless, in relation to the overall number of annual deaths from the two viruses, there has been a decline from the estimates produced by ECDC in 2015 in two out of three countries: 45.0% fewer deaths occurred in Italy and 65.0% fewer in Spain. In Romania the absolute number of deaths has remained largely unchanged [7]. These findings underscore the importance of tailoring public health strategies to local epidemiological contexts.

The study had several strengths of note. This study was the first attempt to implement the WHO protocol with modifications informed by findings from the pilot study [10]. We used a stratified approach to site selection, considering also differences in the epidemiological burden of viral hepatitis infection as reported in different geographical areas in Italy, Romania, and Spain, enabling the recruitment of patients from multiple sites representing sufficient epidemiological and geographical heterogeneity of viral hepatitis. Having a predefined target sample size for each country ensured that the recruited samples enabled reporting results with the desired level of precision. Retrospective patient enrolment was conducted through consecutive inclusion, minimising the risk of selection bias. Furthermore, the introduction of a stepwise approach for selecting patients with decompensated cirrhosis allowed for more precise identification of those at higher risk of mortality, thereby improving the applicability of AFs estimates to mortality data. Weighting AFs against the age and sex structure of Eurostat mortality data for each country has strengthened the accuracy of the results. Unweighted AFs most accurately represent the proportion of incident cases of decompensated cirrhosis and HCC caused by HCV and HBV. In contrast, adjust weighted AFs are a better reflection of the proportion of deaths from these conditions that can be attributed to HCV and HBV.

The main limitations and practical challenges of the study included reliance on retrospective data collection, potential selection bias in site participation and a temporal mismatch between hospital and mortality data. Retrospective data collection required revisiting patient records, a process that is not routinely integrated into institutional workflows and was not only resource intensive but sometimes yielded incomplete information.

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TABLE 3 | Number of deaths with reported primary cause of cirrhosis, HCC, HBV and HCV in Italy, Romania, and Spain, 2022.

Country	Primary cause of deaths	Number of deaths, *n*
Italy	Cirrhosis (ICD-10 codes: K70, K72, K73, K74, K76.0 and I85.0)	5451
	HCC (ICD-10 codes: C22.0 and C22.9)	6166
	HBV (ICD-10 codes: B16.2, B16.9. B18.0 and B18.1)	202
	HCV (ICD-10 code: B17.1 and B18.2)	1140
Romania	Cirrhosis (ICD-10 codes: K70, K72, K73, K74, K76.0 and I85.0)	9308
	HCC (ICD-10 codes: C22.0 and C22.9)	2245
	HBV (ICD-10 codes: B16.0, B16.9. B18.0 and B18.1)	21
	HCV (ICD-10 code: B17.1 and B18.2)	57
Spain	Cirrhosis (ICD-10 codes: K70, K72, K73, K74, K76.0 and I85.0)	4498
	HCC (ICD-10 codes: C22.0 and C22.9)	3061
	HBV (ICD-10 codes: B16.0, B16.2, B16.9, B17.0 B18.0 and B18.1)	52
	HCV (ICD-10 code: B17.1 and B18.2)	225

Abbreviations: B16.0, acute hepatitis B with delta-agent and hepatic coma; B16.2, acute hepatitis B without delta-agent and with hepatic coma; B16.9, acute hepatitis B without delta-agent and without hepatic coma; B17.1, acute hepatitis C; B18.0, Chronic viral hepatitis B with delta-agent (co-infection with hepatitis D); B18.1, Chronic viral hepatitis B without delta-agent; B18.2, Chronic viral hepatitis C; C22.0, liver cell carcinoma (hepatocellular carcinoma); C22.0, liver cell carcinoma (hepatocellular carcinoma); C22.9, malignant neoplasm of liver, not specified as primary or secondary; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; I85.0, oesophageal varices with bleeding; K70, alcoholic liver disease; K72, hepatic failure, not elsewhere classified; K73, chronic hepatitis, not elsewhere classified; K74, fibrosis and cirrhosis of liver; K76.0, fatty (change of) liver, not elsewhere classified.

TABLE 4 | Estimated mortality from HBV and HCV in Italy, Romania and Spain, 2022.

Country	Population as of 1.01.2022	Type of hepatitis	Mortality, absolute number (95% CI)	Mortality, rate per 100 000 (95% CI)
Italy	59 030 000	HBV	1848 (1509–2187)	3.1 (2.6–3.7)
		HCV	6731 (6255–7207)	11.4 (10.6–12.2)
Romania	19 042 000	HBV	2283 (1941–2625)	12.0 (10.2–13.8)
		HCV	2623 (2219–3027)	13.8 (11.7–15.9)
Spain	47 487 000	HBV	283 (161–405)	0.6 (0.3–0.9)
		HCV	1748 (1468–2028)	3.7 (3.1–4.3)

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus.

Nevertheless, the proportion of missing data was relatively low. Missing HBV status data accounted for less than 1% in Spain and Romania and 9.2% in Italy, while missing HCV status data were 0% in Spain, less than 1% in Romania, and 4.5% in Italy. Records with incomplete HBV or HCV information were excluded from the analysis, with no substantial impact on the width of the confidence intervals.

The absence of financial incentives may have contributed to low motivation among medical staff to participate in data collection, limiting access to a comprehensive selection of study sites. As a result, random site selection was not feasible. Instead, a stepwise approach to site selection was employed, with final site inclusion largely dependent on the willingness and availability of healthcare personnel, potentially introducing selection bias. This approach resulted in a suboptimal number of participating sites in Spain, preventing full attainment of the target sample size and consequently affecting the precision of the estimates. These limitations may have affected the interpretation and generalisability of the findings. Furthermore, participating study sites were mostly referral centres more likely to manage advanced disease, introducing a potential referral bias, although this may have been offset by higher quality and completeness of clinical information regarding disease severity and complications.

In addition, we were constrained to use 2022 Eurostat mortality data (the most recent data available at the time), whereas our AFs estimates were derived from 2023 data, resulting in a temporal mismatch. Given the observed downward trend in absolute mortality numbers compared with 2015 estimates, it is likely that 2023 mortality figures would have been even lower. We were also unable to assess the quality of the Eurostat data or to evaluate potential misclassification of cirrhosis, HCC, and viral hepatitis cases. In the second phase of this project as we extend the work across other countries in the region, we plan

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to assess the extent of possible misclassification by comparing Eurostat data with local mortality data sources.

We were also unable to adjust AFs among individuals with multiple aetiologies, as comparable data on the prevalence of alcohol use and metabolic risk factors in the general population without hepatic sequelae were not available. Moreover, current scientific evidence does not allow for a reliable quantification of the relative contribution of individual risk factors to the development of hepatic sequelae and the extent to which these interact in individuals with coexisting aetiologies. Consequently, hepatic sequelae observed in such individuals were attributed to HBV or HCV even when additional risk factors were present, potentially leading to overestimation of AFs. This limitation was only partially addressed through AFs adjustment.

Furthermore, although AFs were weighted against the age and sex structure of mortality data, we lacked information on the age at which these individuals belonging to mortality envelopes were diagnosed with advanced liver disease. This would have provided a more accurate basis for weighting the sample against the age and sex distribution of mortality cases. Further analysis of the data by the time interval between HCV diagnosis, treatment initiation, and the development of liver-related complications could provide valuable insights into the causes of sequelae in case multiple underlying factors are present. The work will be taken forward in the next stage of the project.

In future projects interpretation of HBV-attributable fractions could also be strengthened by systematically capturing hepatitis D virus (HDV) co-infection. This is relevant, since HDV co-infection represents the most severe form of chronic viral hepatitis and substantially accelerates progression to cirrhosis, decompensation, and HCC. The lack of HDV information could impact the estimated HBV-attributable burden, particularly in HDV-endemic settings such as Romania and so should be taken into consideration. Though not directly presented and discussed in this paper, the data on other underlying factors including alcohol and metabolic factors are important to monitor in order to understand more clearly the trends in decompensated cirrhosis and HCC mortality over time. These aspects will be analysed further by country collaborators.

Achieving hepatitis elimination requires countries to meet the WHO 2030 elimination targets, which include a combined mortality rate of ≤ 6 hepatitis C and hepatitis B related deaths per 100 000 population. Monitoring progress towards this target is essential for evaluating hepatitis programme performance and guiding the optimisation of interventions and represents a key component of the WHO validation framework [4]. Therefore, robust data reporting systems capable of estimating AFs should be established. Our experience with project implementation shows that most of the data required to estimate hepatitis-related burden in EU/EEA settings may already be captured in routine patient records. The data collection tool proposed in Appendix S2 could be further simplified to focus exclusively on viral hepatitis. The main challenge for health systems is not the absence of data, but rather the capacity and willingness to leverage existing clinical information for epidemiological purposes. To support this objective, integrating AFs estimation as a routine component of surveillance should be a priority for hepatitis programmes in EU/EEA countries, in line with WHO recommendations, and embedded within existing monitoring systems to help standardise this work and ensure resources get allocated. This involves selecting sentinel centres that treat representative populations of patients with HCC and decompensated cirrhosis, establishing data flows for capturing underlying factors to enable annual AFs assessments, and revising hospital registry variables to enable direct extraction of relevant data while ensuring compliance with data protection regulations. Emphasising the importance of AFs data providing an accurate estimation of hepatitis specific mortality that is essential for assessing national hepatitis responses, together with targeted financial incentives, may increase participation of selected sentinel centres in data collection in the next rounds. Strengthening collaboration with vital statistics registers could also be valuable to incorporate the most recent mortality data to produce HBV and HCV mortality estimates.

6 | Conclusions

This study provided up to date empirical evidence on HBV and HCV attributable mortality from three EU countries, which was used to estimate the mortality in Italy, Romania, and Spain from hepatitis-related liver diseases. Whilst the estimated overall number of deaths related to HBV and HCV has declined in Italy and Spain, as of 2022 all three countries did not achieve the WHO's 2025 interim targset for hepatitis C-related mortality of having no more than 3 deaths per 100 000 people. However, both Italy and Spain met the target for hepatitis B of having less than 7 deaths per 100 000. Overall, these results underscore the importance of sustained efforts to strengthen the prevention and control of viral hepatitis. In this context, the development of integrated surveillance systems capable of estimating AFs on a routine basis, would support the monitoring of liver disease burden and progress towards elimination targets. Such approaches are also aligned with WHO recommendations and reinforce the value of clinical data in informing strategies for liver disease prevention, including HCC.

Author Contributions

Conceptualization: E.D., O.M, J.R.-U., G.M. Methodology: O.K., E.D., H.H.T., O.M, J.R.-U., G.M., J.R., M.-L.J., C.d.M., D.R. Formal Analysis: H.H.T., O.K. Investigation: O.K., E.D., O.M, J.R.-U., G.M., J.R., C.d.M., L.A.K., M.G.Q., B.M., S.R., O.P., D.J., C.C., M.B.F., E.V.-A., A.D. Data Curation: O.K., M.-L.J., H.H.T., L.A.K., M.G.Q., B.M., S.R., M.R., A.D.F., V.Co., S.A., F.M., M.V., A.L., S.F., V.Ca., C.C., F.L., R.C., F.P.R., S.B., N.C., C.S., B.C., M.R.B., O.P., D.J., C.C., L.S.G., M.G., C.E., M.C., R.C., A.T., L.H., C.M., A.P., R.S., C.N., A.P., M.B.F., E.V.-A., A.D., C.F., S.A., A.A., R.B.C. Writing – Original Draft: O.K., E.D., H.H.T., O.M, J.R.-U., G.M., L.A.K., M.G.Q., B.M., S.R., O.P., D.J., C.C., M.B.F., E.V.-A., A.D. Writing – Review and Editing: all. Visualisation: O.K. Supervision: E.D., D.R. Funding Acquisition: E.D.

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Conflicts of Interest

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** List of participating centres and enrolment numbers. **Appendix S2:** Case report form.

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