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ORIGINAL ARTICLE

Observational Study

Sex-based differences in hepatitis delta virus infection: Insights from the Italian PITER hepatitis delta virus cohort

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Abstract

BACKGROUND

Hepatitis delta virus (HDV) infection is the most severe form of chronic viral hepatitis, yet sex-based clinical differences remain poorly defined. Understanding these differences may inform disease management and guide research.

AIM

To investigate sex-related differences in demographic and clinical characteristics of patients with chronic HDV infection in a nationwide, real-world Italian setting.

METHODS

We analyzed demographic, clinical, and virological data from 513 hepatitis B

surface antigen/anti-HDV-positive patients, consecutively enrolled between 2019 and 2024, across 58 liver clinics in the Italian PITER HDV cohort. A propensity score-weighted logistic regression model evaluated the association between sex and cirrhosis and/or hepatocellular carcinoma.

RESULTS

Among 513 patients (61.6% male), median age (56.0 years) and age distribution were similar by sex (P = 0.41). Cirrhosis was frequent: 73.4% *vs* 66.0% (anti-HDV-positive) and 77.8% *vs* 74.2% (HDV RNA-positive) in males and females, respectively. HDV RNA levels were comparable (P = 0.93). The highest proportion of females with cirrhosis (33.8%) was in the 56-60-year group, similar to males (34.9%). Among patients with cirrhosis aged ≤ 40 years, females, (80.9% of whom of non-Italian origin), were more represented than males (16.1% *vs* 6.5% respectively, P < 0.05). Male sex was associated with cirrhosis (odds ratio = 1.85; 95% confidence interval: 1.004-3.40). Among HDV RNA-positive patients, males more often had hepatocellular carcinoma, elevated gamma-glutamyl transpeptidase, alcohol use, diabetes, hypertension, steatotic liver disease, and hepatitis C virus/human immunodeficiency virus coinfection. Interferon eligibility was similar.

CONCLUSION

HDV-infected females develop cirrhosis earlier, without liver disease cofactors, while males show advanced liver disease with multiple cofactors. Tailored care for young migrant women and cofactor-guided management for men may improve HDV outcomes, promoting equity.

Key Words: Hepatitis delta virus; Chronic hepatitis delta virus infection; Cirrhosis; Sex differences; Migrant

Core Tip: This multi-centre study analyzed 513 patients with chronic hepatitis delta virus (HDV) infection, enrolled across 58 Italian liver clinics regardless of treatment eligibility. The study population reflects the current HDV epidemiology in Italy, including a high proportion of migrant women. Key sex-based differences emerged: Men had a greater burden of metabolic comorbidities and hepatocellular carcinoma, while women, particularly those born abroad, were more likely to develop cirrhosis not only after menopause, as seen in other chronic viral liver diseases, but also at significantly young ages, including those younger than 40 years of age. Tailored care for young migrant women, unvaccinated against hepatitis B virus, and cofactor-guided management for men may improve liver disease outcomes.

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INTRODUCTION

Chronic viral hepatitis remains a major global cause of liver-related morbidity and mortality[1-3]. Increasing evidence highlights sex as a critical determinant in the progression and outcomes of these infections, shaping biological susceptibility, age, transmission mode, and also healthcare access and provider response. These differences contribute to disparities in diagnosis, treatment, and outcomes between men and women[4].

In both hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, sex differences influence the clinical course[4-6]. In particular, the protective effects observed in women diminish after menopause, contributing to accelerated liver fibrosis progression in older age[7]. Antiviral response is also modulated by sex, particularly in HCV, where postmenopausal women exhibit reduced sustained virological response to interferon (IFN)-based therapy, likely due to hormonal decline and more advanced liver disease at treatment initiation[8]. In contrast, the influence of sex on hepatitis delta virus (HDV) infection, the most severe form of chronic viral hepatitis, remains poorly understood. Given HDV's highly aggressive nature and its rapid progression to cirrhosis and hepatocellular carcinoma (HCC), elucidating sex-related differences in disease trajectories is essential, particularly in light of emerging therapeutic options[9,10].

This study aimed to investigate sex-based differences in the demographic, clinical, and virological profiles of patients with chronic HDV infection enrolled in the Italian multi-centre PITER HBV/HDV cohort. Specifically, we evaluated whether sex is independently associated with disease severity (cirrhosis and/or HCC) and explored its interplay with age, comorbidities, and viral markers, which may help inform more personalized and equitable approaches to HDV care.

MATERIALS AND METHODS

Study population

This study analyzed cross-sectional baseline data from the PITER HBV/HDV cohort, comprising 5923 hepatitis B surface antigen (HBsAg)-positive patients (aged older than 18 years), consecutively enrolled at 58 Italian referral centres between November 2019 and March 2024. A detailed flow chart outlining the inclusion of patients in this study is provided in Figure 1. Of those screened for HDV (n = 4445; 75% of males, 74.5% of females), 513 anti-HDV-positive patients with complete demographic (age, sex) and core clinical data (cirrhosis staging and HCC diagnosis) were included in the sex-based analysis. Patients without anti-HDV testing, as well as those who tested negative for anti-HDV, were excluded from the analytical cohort. However, for comparative purposes, the prevalence of cirrhosis by age and sex was assessed among HBV-monoinfected individuals (*i.e.*, anti-HDV negative) within the broader HBsAg-positive population of the PITER cohort, based on enrollment (baseline) data.

Data collection

Demographic, clinical, and laboratory data were collected at enrolment *via* a standardized electronic case report form. Cirrhosis was diagnosed by liver histology (Metavir ≥ F4/Ishak ≥ 6), transient elastography [liver stiffness measurements (LSM) > 12.5 kPa], or imaging/clinical signs of portal hypertension. LSM was considered valid if ≥ 10 measurements had a success rate of ≥ 80%, an interquartile range (IQR) of < 30%, and a body mass index (BMI) of < 30 kg/m^2. Liver disease severity was evaluated using the child-Pugh and model for end-stage liver disease (MELD) scores as surrogate markers of hepatic dysfunction. These scoring systems were originally developed for prognostic evaluation but are commonly applied in cross-sectional studies to stratify patients according to the degree of liver functional impairment, without implying predictive intent[11]. In this study, they were used solely to support clinical phenotyping and to describe the severity of hepatic dysfunction at enrollment, including assessment of hepatic functional reserve and the potential presence of portal hypertension, as suggested by clinical and laboratory findings, such as thrombocytopenia[12-14].

Cofactors and comorbidities, potentially related to liver disease progression, included alcohol use, injection drug use, diabetes, hypertension, dyslipidemia, overweight/obesity, and steatosis (diagnosed by ultrasound, magnetic resonance imaging, or biopsy). Steatotic liver disease (SLD) was defined according to the European Association for the Study of the Liver-European Association for the Study of Diabetes-European Association for the Study of Obesity guidelines[15]. Extrahepatic comorbidities, including those contraindicating IFN therapy, were also evaluated. Among HDV RNA-positive patients, potential eligibility for IFN-based therapy was evaluated based on medical contraindications, excluding considerations of treatment adherence or patient willingness, as previously described[9].

Routine serological and virological testing, including HBsAg, hepatitis B e antigen/anti-hepatitis B e antigen, and anti-HDV, anti-HCV, and anti-human immunodeficiency virus (HIV) antibodies, was performed using commercial enzyme immunoassays. When indicated, HCV RNA and HIV RNA were measured using standard assays.

Quantitative HDV RNA was assessed using the RoboGene HDV RNA quantification kit 2.0 (limit of detection = 6 IU/mL; Robogene GmbH, Germany) in 78% of patients, and in the remaining patients using other commercial assays. Results in copies/mL were converted to IU/mL. Data quality was ensured by remote monitoring and query resolution.

Statistical analysis

The analysis examined sex-related differences among HBsAg/anti-HDV-positive patients and in those HDV RNA-positive. To ensure data integrity while reflecting the observational nature of the study, only patients with complete core demographic, virological, and clinical data relevant to the study objectives (including age, sex, cirrhosis status, and HCC diagnosis) were included in the analyses, even when some secondary clinical or laboratory parameters were incomplete or missing. No imputation procedures were applied. Proportions are based on available data, and totals may differ due to missing values. Continuous variables were reported as medians with IQRs, categorical variables as counts and percentages. Clinically relevant cut-offs for platelet count (≤ 150000 μL), child-Pugh class (A *vs* B and C), and MELD score (≥ 20) were used to describe the liver disease severity of the enrolled patients. Comparisons between groups were performed using χ^2 or Fisher's exact tests for categorical variables, and the Mann-Whitney U test for continuous variables. The association between sex and the selected outcome (cirrhosis and/or HCC) was evaluated by odds ratios (ORs) and its 95% confidence intervals (CIs).

To control for confounding due to baseline differences between males and females, we applied a propensity score-based inverse probability weighting (IPW) method[16,17]. The propensity score, defined as the probability of being male (*vs* female) given the observed covariates, was estimated using a probit regression model, which is suitable for the binary nature of the exposure variable (sex). Covariates included in the model were: Age, BMI category, HDV RNA status, HBV DNA detectability, history of IFN therapy, duration of nucleos(t)ide analogue (NUC) therapy, alcohol use, diabetes, and presence of SLD. The quality of the balancing procedure was evaluated using standardized mean differences, with values < 0.10 indicating adequate balance. Following IPW adjustment, a logistic regression model was applied to assess the independent association of sex with cirrhosis and/or HCC. Statistical significance was evaluated using the Wald test with a two-sided P value. P values < 0.05 were considered statistically significant. Statistical analyses were conducted using STATA version 16.1 (StataCorp, College Station, TX, United States).

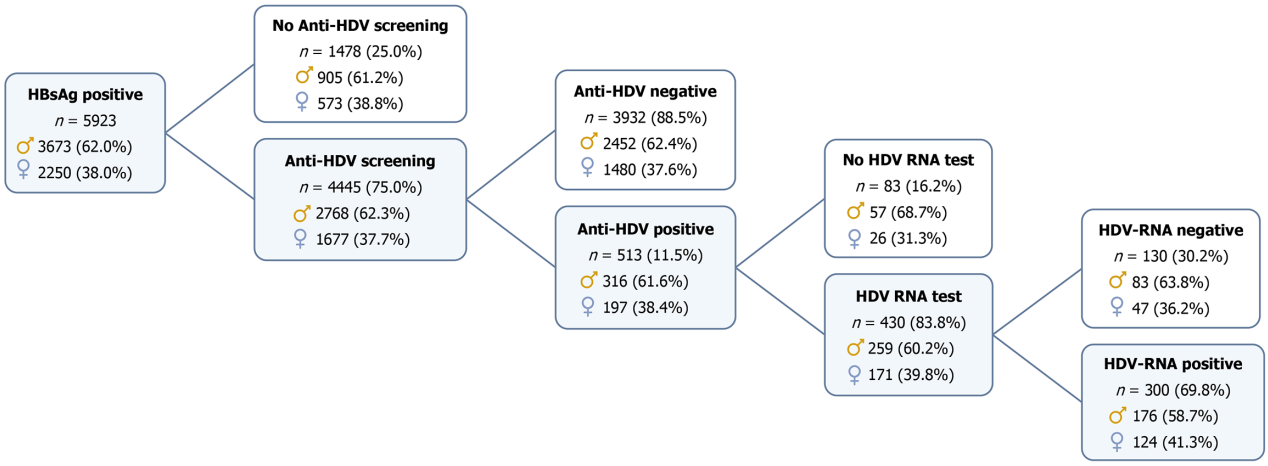


Figure 1 Flow chart of the patients enrolled in the study. HBsAg: Hepatitis B surface antigen; HDV: Hepatitis delta virus.

RESULTS

Characteristics of the study population by sex

The main characteristics of the study population, categorized by sex, are presented in Table 1. Among the 513 HBsAg/anti-HDV-positive patients (none of whom were on bulevirtide treatment at enrollment), 316 (61.6%) were male and 197 (38.4%) were female. Median age was 56.0 years for both sexes (P = 0.41). Non-Italian origin (33.7%) was significantly more common among females (46.7%) than among males (25.6%, P < 0.001), with most foreign-born patients coming from Central and Eastern Europe, followed by sub-Saharan Africa and Asia (detailed demographic and clinical characteristics by nationality are reported in Supplementary Table 1).

Cirrhosis affected over 70% of patients, with a slightly higher, but not statistically significant, prevalence in males (73.4%) than females (66.0%, P = 0.073). Thrombocytopenia (platelet count ≤ 150000/μL) affected 55.5% of the patient population, with no sex differences. Elevated gamma-glutamyl transpeptidase (GGT) was more frequent in males (46.6% *vs* 27.3%, P < 0.0001), suggesting greater biochemical liver injury. Alanine transaminase (ALT) elevation was higher in men, with a non-significant, but borderline statistically significant difference (P = 0.065), which may still reflect clinically relevant trends in hepatocellular injury between the sexes (Table 1). HCC was diagnosed in 9.8% of patients with a significantly higher rate in males (12.6%) compared to females (5.6%, P = 0.01). Most patients were on NUC therapy at enrolment (72.5%), with similar proportions by sex and median treatment duration of 4.2 years (Table 1).

Risk factors and comorbidities

As shown in Table 1, behavioral risk factors were significantly more prevalent in males, including injection drug use, alcohol consumption, and co-infection with HCV or HIV (all P ≤ 0.001). Males also showed higher rates of diabetes (P = 0.002) and SLD (P = 0.031). Obesity was more frequent in females (15.4% *vs* 8.6%), but the difference was not statistically significant (P = 0.124) (Table 1). Among those with SLD, alcohol use was significantly more frequent in males (39 out of 84; 46.4%) than in females (4 out of 36; 11.1%) (P = 0.001).

Cirrhosis and age distribution patterns by sex

Sex-specific age distribution patterns and demographic and clinical characteristics among patients with cirrhosis (n = 362; 64.1% male) are summarized in Table 2 and Figure 2. Among these patients, non-Italian origin was significantly more common in females than in males (40.8% *vs* 23.7%; P = 0.001). Most patients with cirrhosis in both sexes (59.9% of males and 67.7% of females) were younger than 61 years. Among females with cirrhosis, the highest proportion (33.8%) was in the 56-60-year age group, closely matching that of males (34.9%) (Table 2 and Figure 2). However, in the ≤ 40-year age group, a significantly higher proportion of females were observed compared to males (16.1% *vs* 6.5%, P = 0.003); 80.9% of these younger females were of non-Italian origin.

Patients with HBV mono infection enrolled in the PITER HBV cohort during the same period had a significantly lower overall prevalence of cirrhosis compared to HDV-coinfected patients (24.1% *vs* 70.6%, P < 0.001; specific data from the HBV cohort are not shown). Among HBV-mono infected individuals (PITER HBV cohort), cirrhosis was more prevalent in males than females (28.0% *vs* 15.6%, P < 0.001), yet in both sexes it occurred predominantly after the age of 55. This pattern contrasts with the earlier onset and more aggressive liver involvement observed in HDV coinfection, which disproportionately affects younger individuals, particularly females of non-Italian origin (Figure 2).

Sex-based differences in HDV RNA-positive patients

Of the 513 anti-HDV-positive individuals, 430 (83.8%) were tested for HDV RNA. Testing rates were similar in males and females, with 18% of males and 13% of females remaining untested (P = 0.148). Among those tested, HDV RNA was detectable in 68.0% of males and 72.5% of females (P = 0.314) (Table 1).

Table 1 Characteristics of hepatitis B surface antigen +/anti-hepatitis delta virus positive patients by sex, *n* (%)

	Anti-HDV positive		*P* value
	Males	Females	
	316[1] (61.6)	197[1] (38.4)	0.738
Age, median (Q1-Q3)	56 (48-63)	56 (45-62)	0.409
≤ 40	35 (11.1)	37 (18.8)	0.143
41-50	59 (18.7)	38 (19.3)	
51-60	114 (36.1)	58 (29.4)	
61-70	85 (26.9)	50 (25.4)	
> 70	23 (7.3)	14 (7.2)	
Non-Italian natives	81 (25.6)	92 (46.7)	< 0.001
Injection drug use (any time)	45 (17.3)	3 (1.7)	< 0.001
ALT > 35 IU/L	199 (64.8)	108 (56.5)	0.065
GGT > 50 IU/L	116 (46.6)	44 (27.3)	< 0.001
HBeAg positive	16 (5.3)	12 (6.3)	0.612
HDV RNA positive (*n* = 430 tested)	176 (68.0)	124 (72.5)	0.314
Cirrhosis	232 (73.4)	130 (66.0)	0.073
Child-Pugh class			
A	197 (86.8)	103 (82.4)	0.231
B	25 (11.0)	21 (16.8)	
C	5 (2.2)	1 (0.8)	
MELD ≥ 20	6 (3.0)	0 (0.0)	0.097
HCC	40 (12.6)	11 (5.6)	0.010
PLT ≤ 150000	177 (57.8)	108 (56.5)	0.776
Previous IFN	104 (35.4)	49 (27.7)	0.084
Cofactors of liver disease			
BMI 25-30	84 (37.8)	45 (33.1)	0.124
BMI ≥ 30	19 (8.6)	21 (15.4)	
Ongoing alcohol use	61 (23.0)	10 (6.1)	< 0.001
Past use	58 (21.9)	15 (9.2)	
Diabetes	28 (8.9)	4 (2.0)	0.002
Steatotic liver disease	84 (26.6)	36 (18.3)	0.031
Anti-HCV positive (all HCV RNA negative)	42 (14.7)	1 (0.6)	< 0.001
Anti-HIV positive	22 (8.1)	1 (0.6)	0.001
NUC treatment			
Ongoing NUC therapy	234 (74.3)	138 (70.4)	0.338
Years of NUC therapy, median (Q1-Q3)	4.2 (1.7-7.9)	4.2 (2.0-7.6)	0.733

[1]Proportions are based on available data. Inconsistencies are due to missing values.

HDV: Hepatitis delta virus; ALT: Alanine transaminase; BMI: Body mass index; GGT: Gamma-glutamyl transpeptidase; HBeAg: Hepatitis Be antigen; HCC: Hepatocellular carcinoma; MELD: Model for end-stage liver disease; IFN: Interferon; PLT: Platelet; Q1: Quarter 1; Q3: Quarter 3; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; NUC: Nucleos(t)ide analogue.

Table 2 Characteristics of hepatitis B surface antigen +/anti-hepatitis delta virus positive patients with F4/cirrhosis by sex, *n* (%)

Characteristics	F4/cirrhosis		*P* value
	Males (*n* = 232[1])	Females (*n* = 130[1])	
Age, median (Q1-Q3)	57 (50-64)	57 (46-62)	0.163
≤ 40	15 (6.5)	21 (16.1)	0.052
41-50	43 (18.5)	23 (17.7)	
51-60	81 (34.9)	44 (33.8)	
61-70	73 (31.5)	34 (26.1)	
> 70	20 (8.6)	8 (6.1)	
Non-Italian natives	55 (23.7)	53 (40.8)	0.001
Injection drug use (any time)	31 (16.4)	3 (2.6)	< 0.001
Liver biopsy (any time)	58 (30.2)	30 (28.0)	0.693
ALT > 35 IU/L	152 (67.9)	83 (65.3)	0.632
GGT > 50 IU/L	101 (55.8)	40 (38.1)	0.004
HBeAg positive	10 (4.5)	9 (7.2)	0.289
HDV-RNA tested	193 (83.2)	114 (87.7)	0.252
HDV-RNA positive	137 (71.0)	92 (80.7)	0.059
HDV RNA, median (Q1-Q3)	95614 (3096-1000000)	34563 (3971-377359)	0.932
Child-Pugh class			
A	197 (86.8)	103 (82.4)	0.231
B	25 (11.0)	21 (16.8)	
C	5 (2.2)	1 (0.8)	
MELD ≥ 20	6 (3.0)	0 (0.0)	0.097
HCC	38 (16.5)	11 (8.6)	0.036
PLT ≤ 150000	166 (74.1)	100 (78.7)	0.330
Previous IFN	75 (34.6)	35 (29.7)	0.362
Cofactors of liver disease			
Ongoing alcohol use	39 (19.8)	3 (2.6)	< 0.001
Past use	50 (25.4)	11 (9.6)	
BMI 25-30	61 (38.4)	27 (31.0)	0.385
BMI ≥ 30	15 (9.4)	12 (13.8)	
Diabetes	22 (9.5)	2 (1.5)	0.004
Steatotic liver disease	63 (27.2)	23 (17.7)	0.042
Anti-HCV positive (all HCV RNA negative)	33 (15.9)	1 (0.9)	< 0.001
anti-HIV positive	14 (7.1)	1 (1.0)	0.024
NUC treatment			
Ongoing NUC therapy	186 (80.5)	102 (79.1)	0.742
Years of NUC therapy, median (Q1-Q3)	4.8 (1.5-8.2)	4.3 (2.1-7.7)	0.683

[1]Proportions are based on available data. Inconsistencies are due to missing values.

HDV: Hepatitis delta virus; ALT: Alanine transaminase; BMI: Body mass index; GGT: Gamma-glutamyl transpeptidase; HBeAg: Hepatitis Be antigen; HCC: Hepatocellular carcinoma; MELD: Model for end-stage liver disease; IFN: Interferon; PLT: Platelet; Q1: Quarter 1; Q3: Quarter 3; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; NUC: Nucleos(t)ide analogue.

Demographic and clinical characteristics of HDV-RNA-positive patients, stratified by sex, are presented in Table 3. Notably, among participants aged 40 years or younger, females were more frequently represented than males (23.4% *vs* 13.1%), and this was the only age group in which females outnumbered males. HDV RNA levels were comparable between sexes ($P = 0.932$) (Table 3), irrespective of nationality (Supplementary Table 1) or cirrhosis status (Table 2).

ALT elevations were similarly distributed between sexes, while GGT abnormalities were significantly more common in males (57.7%) than females (34.0%, $P < 0.001$). Cirrhosis was present in 76.3% of HDV RNA-positive patients, with no sex difference (77.8% males *vs* 74.2% females). Child-Pugh class and thrombocytopenia rates were comparable between groups ($P > 0.05$). In contrast, HCC prevalence among viremic patients was significantly higher in males (17.9%) than in females (5.8%, $P = 0.002$) (Table 3).

Among HDV RNA-negative patients ($n = 130$), cirrhosis was still common ($n = 78$, 60.0%), especially in males (67.5% *vs* 46.8.% in females; $P = 0.02$). HCC was diagnosed in 6 HDV RNA-negative males and one HDV RNA-negative female (Supplementary Table 2). Among viremic patients, the detectability of HBV DNA did not differ by sex, regardless of NUC therapy (Supplementary Table 3).

Propensity score analysis: Sex and clinical outcomes

After adjustment for covariates through propensity score weighting and excluding patients with HCV and/or HIV coinfection, male sex remained independently associated (OR = 1.85; 95%CI: 1.004-3.40) with the presence of cirrhosis and/or HCC in chronic HDV infection (Table 4).

Comorbidity profile and IFN eligibility

The comorbidity profile of patients with active infection, according to sex, is shown in Figure 3, and the respective absolute values are reported in Supplementary Table 4. Males had a significantly higher prevalence of key cofactors associated with liver disease progression: Alcohol use ($P < 0.001$), diabetes ($P = 0.003$), hypertension ($P = 0.032$), SLD ($P = 0.015$), and HCV coinfection ($P < 0.001$). HIV coinfection was more common in males, although the difference was not statistically significant ($P = 0.087$). Rates of overweight/obesity and dyslipidemia were similar. At least one comorbidity was present in 48.4% of males and 41.9% of females with active HDV infection (Figure 4). Among 300 patients with active infection, 52.7% were potentially eligible for IFN-based therapy, with no significant sex differences (55.7% of males *vs* 48.4% of females; $P = 0.45$). Absolute contraindications were present in 36.4% of males and 41.9% of females, while relative contraindications were reported in 8.0% and 9.7%, respectively (Figure 4).

DISCUSSION

Sex-specific characteristics in HDV infection remain underexplored in the literature[18]. Our analysis of 513 HBsAg/anti-HDV-positive individuals consecutively enrolled in the Italian multi-centre PITER HBV/HDV cohort (2019-2024) addresses this gap, providing a detailed overview of the evolving epidemiological and clinical landscape. This multi-centre study analyzed 513 patients with chronic HDV infection, enrolled across 58 Italian liver clinics, regardless of treatment eligibility[9]. Key sex-based differences emerged: Men exhibited a higher burden of metabolic comorbidities and HCC, whereas women, especially those born abroad, were more likely to develop cirrhosis not only after menopause, as observed in other chronic viral liver diseases, but also from a notably younger age, with cases emerging even before 40 years[4,5,7].

Notably, among patients under 40 years of age, only 2.1% were Italian-born, whereas 37.6% were non-Italian natives. This likely reflects the enduring impact of Italy's hepatitis B vaccination strategy, introduced in 1991 to target newborns and 12-year-olds, with continued coverage in subsequent birth cohorts and targeted pregnancy screening. HBV screening among women of childbearing age may have contributed to the disproportionately higher representation of non-Italian females (46.7%) compared to males (25.6%, $P < 0.001$). A similar pattern of higher female representation among individuals living with HDV infection was observed in a cohort from Romania[19]. In contrast, male predominance in HDV infection has been observed in other studies, often conducted in different regions or clinical contexts[20,21]. Several factors may account for these discrepancies, including geographic heterogeneity in the migrant population, 85.2% originating from Eastern Europe (mainly Moldova, Romania, and Albania), with smaller proportions from sub-Saharan Africa (7.7%) and Asia (2.1%) in our study. Differences in national HBV vaccination policies and their historical implementation across countries likely contribute to varying patterns of HDV exposure and infection by sex. Additionally, as specialized referral centres, the clinics participating in this study may have enrolled a higher proportion of patients with advanced liver disease, in contrast to population-based screening studies in migrant populations[20,21].

Male patients exhibited a higher prevalence of behavioral and metabolic risk factors, including alcohol use, intravenous drug use, diabetes, and HCV/HIV coinfections, which may explain their greater liver injury (as reflected by elevated GGT) and higher HCC risk[14].

While the overall prevalence of cirrhosis was high in both sexes (73.4% in males and 66.0% in females), age-stratified analysis revealed a notable and potentially significant clinical difference. Although the highest proportion of cirrhosis cases in both sexes occurred in the 56-60-year age group (33.8% in females, 34.9% in males), females, most of whom were of non-Italian origin (80.9%), were significantly more represented than males in the subgroup under 40 years of age (16.1% *vs* 6.5%, $P < 0.05$). For comparison, in the HBV mono infected cohort, analysis of enrollment (baseline) data revealed that cirrhosis was uncommon before age 55 in both sexes, consistent with the generally protective effect of younger age, particularly in females, where the increased risk typically emerged after menopause[4,7]. As reported in the literature, a similar age-related pattern to that observed in HBV monoinfection has also been described in HCV mono

Table 3 Characteristics of hepatitis delta virus-RNA positive patients by sex, *n* (%)

Characteristics	HDV-RNA positive		*P* value
	Males (*n* = 176[1])	Females (*n* = 124[1])	
Age, median (Q1-Q3)	55 (46.5-63)	56 (43.5-62.5)	0.599
≤ 40	23 (13.1)	29 (23.4)	0.226
41-50	37 (21.0)	23 (18.5)	
51-60	54 (30.7)	31 (25.0)	
61-70	48 (27.3)	31 (25.0)	
> 70	14 (7.9)	10 (8.1)	
Non-Italian natives	55 (31.2)	65 (52.4)	< 0.001
HDV RNA, median (Q1-Q3)	66457 (1720-669213)	50739 (4060.9-372159)	0.932
ALT > 35 IU/L	138 (81.2)	87 (73.1)	0.104
GGT >50 IU/L	79 (57.7)	33 (34.0)	< 0.001
HBeAg positive	8 (4.7)	9 (7.6)	0.316
Cirrhosis	137 (77.8)	92 (74.2)	0.464
Child-Pugh class			
A	119 (87.5)	77 (88.5)	> 0.999
B	16 (11.8)	10 (11.5)	
C	1 (0.7)	0 (0.0)	
MELD ≥ 20	3 (2.6)	0 (0.0)	0.284
HCC	31 (17.9)	7 (5.8)	0.002
PLT ≤ 150000	103 (61.3)	76 (63.9)	0.660
Previous IFN	64 (39.5)	33 (30.0)	0.108
NUC treatment			
Ongoing NUC therapy	137 (78.3)	90 (73.2)	0.308
Years of NUC therapy, median (Q1-Q3)	4.1 (1.6-7.4)	4.2 (2.1-7.2)	0.653

[1]Proportions are based on available data. Inconsistencies are due to missing values.
HDV: Hepatitis delta virus; ALT: Alanine transaminase; GGT: Gamma-glutamyl transpeptidase; HBeAg: Hepatitis Be antigen; HCC: Hepatocellular carcinoma; MELD: Model for end-stage liver disease; IFN: Interferon; PLT: Platelet; Q1: Quarter 1; Q3: Quarter 3; NUC: Nucleos(t)ide analogue.

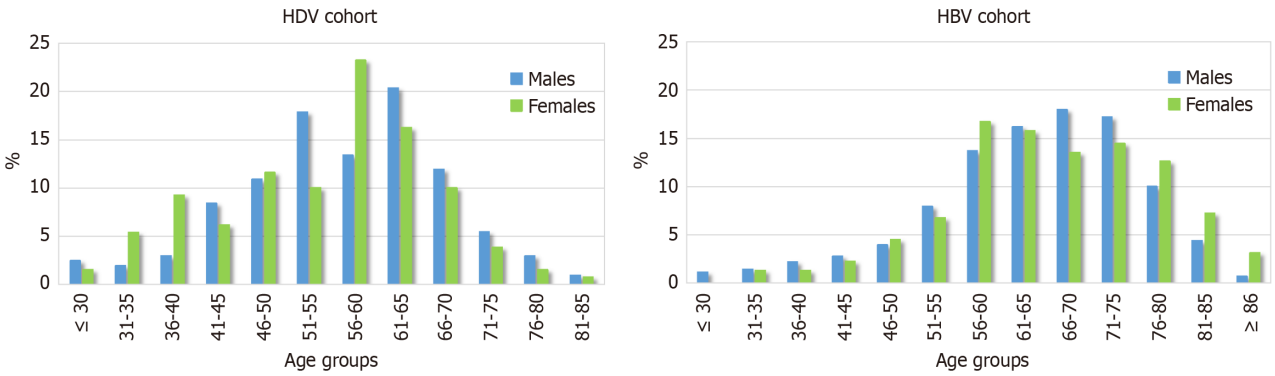


Figure 2 Age distribution in hepatitis B surface antigen +/anti-hepatitis delta virus positive and hepatitis B surface antigen +/anti-hepatitis delta virus negative patients with cirrhosis by sex. HDV: Hepatitis delta virus; HBV: Hepatitis B virus.

Table 4 Propensity score analysis and weighted logistic regression model

Balanced variables	Unweighted (std-diff)	Weighted (std-diff)	*P* value
Age (Ref. ≤ 55 years)	0.1229701	-0.0728242	
HDV-RNA (Ref. neg)	0.1365088	-0.013608	
HBV DNA (Ref. neg)	0.0022074	-0.0190112	
Previous IFN (Ref. no IFN)	0.0422737	-0.0327822	
Years of NUC therapy (continuous variable)	-0.077061	0.0570684	
Alcohol use (Ref. no alcohol)	-0.6436189	0.0261042	
Diabetes (Ref. no diabetes)	-0.1993716	-0.0714145	
BMI 25-30 (Ref. < 25)	-0.0935022	-0.0181635	
BMI ≥ 30 (Ref. < 25)	0.0949776	-0.0145787	
Multivariable analysis	OR	95%CI	
Sex (Ref. female)	1.85	1.004-3.40	0.048

Outcome: Cirrhosis/hepatocellular carcinoma. Study population: Hepatitis B surface antigen +/anti-hepatitis delta virus positive patients, excluding patients coinfected by human immunodeficiency virus and hepatitis C virus. BMI: Body mass index; CI: Confidence interval; HDV: Hepatitis delta virus; HBV: Hepatitis B virus; IFN: Interferon; neg: Negative; NUC: Nucleos(t)ide analogue; OR: Odds ratio; Std-diff: Standardized difference.

infection[8]. In contrast, among HDV-infected women, cirrhosis was more frequently observed at younger ages, suggesting a more aggressive disease course and a potential loss of the sex and age-related protective effect seen in HBV as well as in HCV mono infections[7].

Among patients tested for HDV RNA, viremia was detected at similar rates in males and females (68.0% *vs* 72.5%). However, among HDV RNA-positive individuals, a higher proportion of females were under 40 years of age compared to males (23.4% *vs* 13.1%). Although not statistically significant, this raises the hypothesis of sex-based differences in immunological, hormonal, or viral-host dynamics, warranting further exploration.

In our study population, cirrhosis was also common among HDV RNA-negative patients (60.0%), with a significantly higher prevalence in males than females (67.5% *vs* 46.8%). Several mechanisms may explain this observation. HDV viremia is dynamic, with 20%-25% of chronic HDV patients experiencing spontaneous RNA decline or clearance over time, while still displaying signs of advanced liver injury[22-25]. A single negative HDV RNA test does not exclude prior periods of active replication. This supports the need for serial, standardized HDV RNA monitoring to assess disease activity better and inform treatment decisions[14]. Moreover, HDV is recognized as a highly pathogenic virus, capable of inducing rapid fibrotic progression, even in early stages of infection, as first described by Rizzetto[10] and Rizzetto *et al* [26] and later confirmed by clinical studies and guidelines[14]. As such, the presence of cirrhosis in RNA-negative individuals may reflect long-standing liver damage from previous HDV-active phases, even if viral replication becomes undetectable later[14,22-25,27].

The high prevalence of advanced cirrhosis (child-Pugh B/C) in HDV-infected females underscores the importance of clinical awareness of disease severity in women, even at premenopausal ages. Although younger women bore a greater burden of cirrhosis, HCC was significantly more frequent in men with chronic HDV infection (12.9% *vs* 5.7%), particularly among HDV RNA-positive patients (17.9% *vs* 5.8%, $P = 0.002$). Six HCC cases also occurred in HDV RNA-negative males, and one case was reported in an HDV RNA-negative female. These patterns may reflect a higher prevalence of hepatotoxic exposures and metabolic comorbidities in men. Estrogen's protective effects may contribute to the lower risk of HCC observed in women, even among those with cirrhosis[4].

The early onset of cirrhosis in women, particularly those under 40 and of non-Italian origin, represents a novel and clinically relevant observation. While our propensity score-adjusted analysis identified male sex as an independent predictor of cirrhosis and/or HCC, the disproportionate burden observed among younger females points to a potentially distinct disease trajectory that warrants further investigation. Although the association between male sex and cirrhosis and/or HCC reached statistical significance, the proximity of the *P* value to 0.05 and the lower bound of the CI near 1.0 indicate that this finding should be interpreted with caution and confirmed in future studies. Taken together, these findings highlight the complexity of sex-specific patterns in HDV-related liver disease and support the need for sex-stratified longitudinal studies to validate these differences, elucidate underlying mechanisms, and potentially inform tailored clinical strategies.

The role of HBV replication in HDV disease progression should not be underestimated[28,29]. In this patient population, over 70% of both sexes received NUC therapy, with a higher proportion of males achieving undetectable HBV DNA, though the difference was not statistically significant. These findings may reflect challenges in treatment adherence among females and underscore the need for targeted health literacy interventions, particularly for migrant and vulnerable populations.

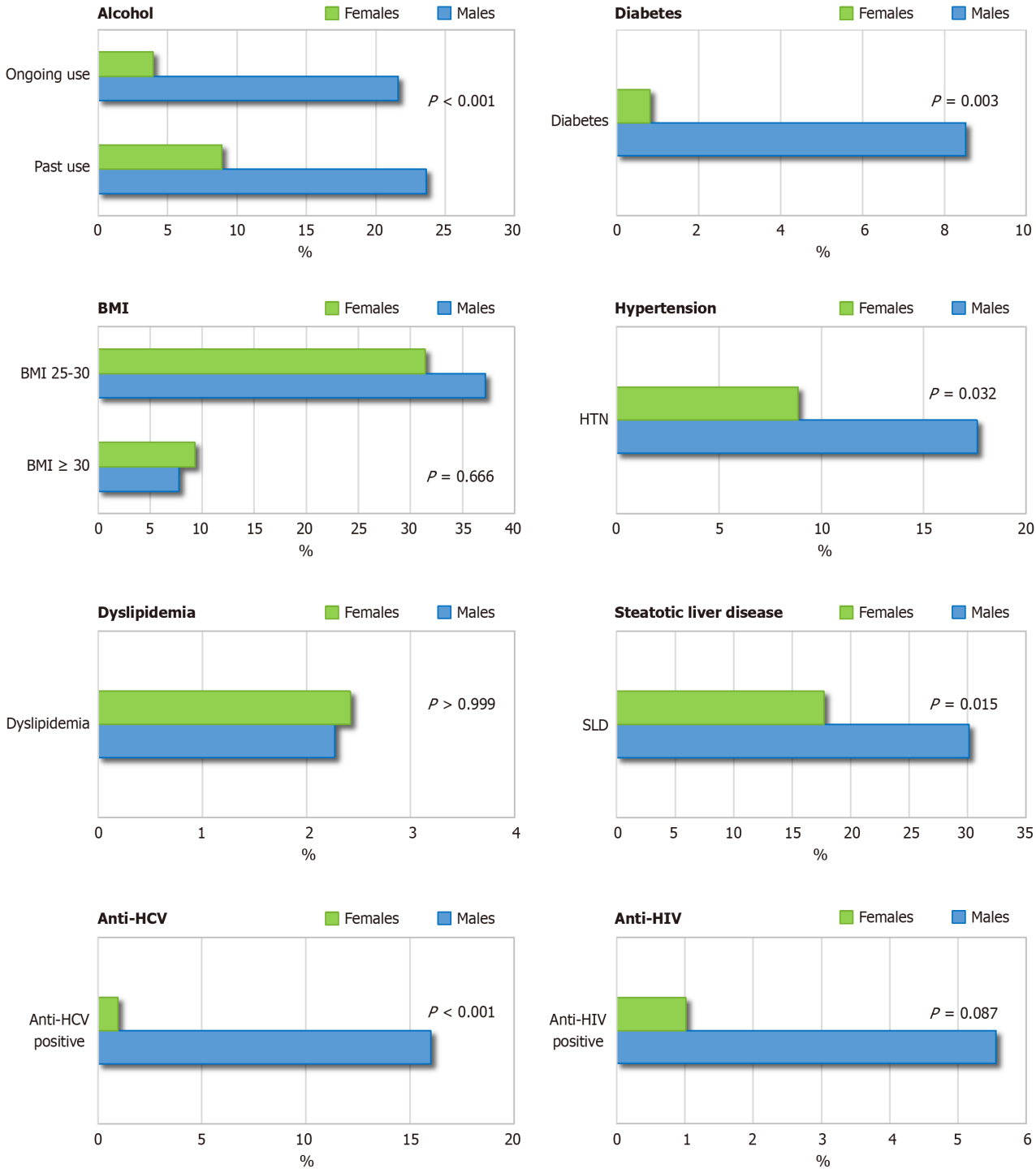
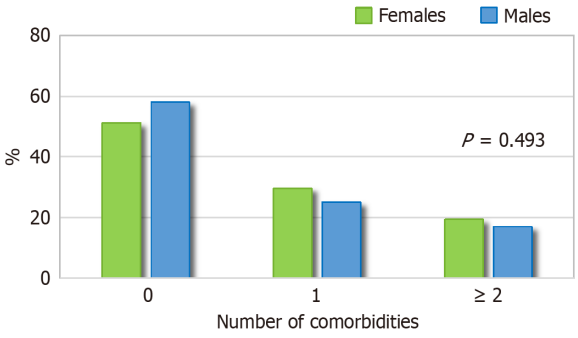


Figure 3 Cofactors for liver disease progression in hepatitis delta virus-RNA positive patients by sex. BMI: Body mass index; HTN: Hypertension; SLD: Steatotic liver disease; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus.

In evaluating treatment history within this cross-sectional analysis, it is essential to note that the enrollment period preceded the approval of bulevirtide; consequently, its use was not assessed at baseline. Among the therapies available at the time of enrollment, previous exposure to IFN-based treatment was somewhat more frequent in males than in females (35.4% *vs* 27.7%; $P = 0.084$), potentially reflecting historical differences in clinical decision-making or treatment acceptance by sex. Notably, the proportion of patients meeting eligibility criteria for IFN therapy, defined by the absence of absolute or relative contraindications due to comorbidities[9], was comparable between sexes, indicating similar baseline clinical suitability for IFN-based regimens. Treatment with bulevirtide and other subsequently introduced therapies is being captured through the ongoing prospective follow-up of the cohort. This baseline evaluation thus provides a critical reference framework for investigating sex-related differences in treatment response, particularly as bulevirtide use expands within the cohort over time.



Controindications to interferon therapy in HDV RNA positive patients[1]

	Males		Females		
	N.	%	N.	%	*P*
Absolute contraindications[2]	64	36.4	52	41.9	0.457
Relative contraindications[3]	14	8.0	12	9.7	
Eligible to PEG-IFN	98	55.7[4]	60	48.4[5]	

Figure 4 Number of comorbidities by sex in hepatitis delta virus-RNA positive patients and their eligibility for peg-interferon. [1]Estimated by the presence of liver-related contraindications and extra-hepatic comorbidities. [2]Absolute contraindications: Child-Pugh class B/C cirrhosis; Child-Pugh class A cirrhosis with portal hypertension (ascites, esophageal varices, platelets < 100000/μL); Portal thrombosis; Autoimmune diseases (hepatitis, systemic lupus erythematosus, rheumatoid arthritis, thyroiditis); Psychiatric disturbances; Ischemic heart disease; Ischemic brain disease; Inflammatory bowel disease; Celiac disease; Psoriasis; Solid tumors under chemotherapy. [3]Relative contraindications: Age ≥ 70 years; Renal failure grade 4-5; Thalassemia trait; Nasal lymphoma. [4]Among these male patients, 39.8% had received interferon therapy. [5]Among these female patients, 31.5% had received interferon therapy. HDV: Hepatitis delta virus; IFN: Interferon.

Strengths and limitations

This study benefits from its large, multicenter design and robust statistical approach, including propensity score adjustment. However, its cross-sectional nature limits the ability to make causal inferences. As in other real-world cohorts, underdiagnosis of HDV remains a challenge: Approximately 25% of HBsAg-positive individuals were not screened for HDV, with no sex-based differences in testing rates, consistent with previous reports[23,30].

HDV RNA testing increased from 62%-84% between 2019 and 2024 (data not shown), paralleling the broader availability of standardized assays, notably RoboGene 2.0, which was used in 78% of the tested patients[9]. Nonetheless, the use of various assays with differing sensitivities may have introduced bias in the assessment of viremia.

In addition, the duration of HBV infection and HDV coinfection, which were not systematically captured in our cohort, may act as unmeasured confounders influencing liver disease progression. This limitation is particularly relevant when interpreting age-related cirrhosis distribution, especially among younger female patients. It may introduce bias if differences in age at HDV acquisition or HBV exposure are not accounted for.

Furthermore, to address baseline imbalances between sexes and reduce confounding, we applied IPW based on propensity scores. This method was chosen for its capacity to adjust for multiple confounders in large observational datasets involving non-randomized groups, such as sex-based comparisons. By balancing baseline characteristics across groups, IPW removes confounding in estimating exposure-outcome associations. Unlike matching or stratification, IPW retains the full sample size and provides a framework for estimating average effects[16,17]. We acknowledge that its validity depends on the absence of unmeasured confounding and that it can be sensitive to extreme weights; to address this, we applied weight stabilization and assessed covariate balance using standardized mean differences.

Finally, while this analysis focused on clinical and epidemiological patterns, unmeasured factors, such as ethnicity and socioeconomic status, as well as healthcare access, particularly among migrant women, may also influence outcomes and warrant further study. Continued prospective follow-up of this cohort will be critical to clarify the long-term impact of sex, age, viral activity, and comorbidities on HDV disease progression.

CONCLUSION

The sex-based differences observed in this study suggest distinct clinical patterns in HDV infection, with women potentially progressing to cirrhosis from young age and showing a peak at postmenopause age, often in absence of known cofactors for liver disease progression. Men more commonly had advanced liver damage, potentially linked to multiple risk factors. Contrary to trends in other chronic viral liver diseases, young female sex may not be protective in HDV. These findings call for greater clinical attention to young, migrant women, particularly those from countries without early HBV vaccination programs, who may be at risk of delayed diagnosis and suboptimal care. Recognizing sex as a potential determinant of HDV progression supports the need for sex-informed approaches in clinical management and risk assessment.

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FOOTNOTES

Author contributions: Kondili LA, Brunetto MR, Coco B, Quaranta MG, and Gaeta GB conceptualized the study and prepared the original draft; Quaranta MG, Tosti ME and Ferrigno L performed the formal analysis and investigation; Villa E, Brancaccio G, Ciancio A, Coppola C, Messina V, Gentile I, Claar E, Morisco F, Santantonio T, Viganò M, Cacciola I, Pompili M, Russo FP, Izzi A, Niro GA, Coppola N, Soria A, Federico A, Morsica G, Puoti M and Lampertico P contributed to review and editing; Kondili LA, and Villa E acquired funding; Coco B, Brancaccio G, Ciancio A, Coppola C, Messina V, Gentile I, Claar E, Morisco F, Santantonio T, Viganò M, Cacciola I, Pompili M, Russo FP, Izzi A, Niro GA, Coppola N, Soria A, Federico A, Morsica G, Puoti M, Lampertico P, Brunetto MR and the PITER Collaborating Investigators provided resources; Kondili LA supervised the project; all authors read and approved the final manuscript.

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Institutional review board statement: The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The study protocol was approved on 24 July 2019 by the National Ethical Committee of the Istituto Superiore di Sanità (CEN), as well as by the Ethics Committees of all participating centres. Patient data were evaluated through pseudonymous analysis using codes generated by electronic case report forms. Compliance with applicable data protection regulations, including the EU General Data Protection Regulation, was confirmed by the Data Protection Officer of the Istituto Superiore di Sanità.

Informed consent statement: All patients provided written informed consent to participate in the study.

Conflict-of-interest statement: These authors disclose the following: Kondili LA has received research grant from Gilead Sciences; Brunetto MR has served as advisory board member for AbbVie, Gilead Sciences, Janssen, Roche and speaker for AbbVie, Gilead Sciences, EISAI-MSD; Quaranta MG has received research grant from Gilead Sciences; Gentile I has received consultant honoraria from MSD, AbbVie, Gilead Sciences, Pfizer, GSK, Astrazeneca, Basilea, SOBI, Nordic/Infecto Pharm, Angelini, Moderna, Shionogi, Advanz Pharma, Abbottand Mundipharma Pharmaceuticals as well as has received departmental grants from Gilead Sciences and Advanz Pharma; Santantonio TA has received speaker honorarium and travel support from Gilead Sciences and Abbvie; Viganò M has served as Advisory Board/Speaker Bureau for Gilead Sciences, AbbVie, Kedrion, IPSEN; Soria A has received speaker honorarium, travel support and research funding from AbbVie and Gilead Sciences; Puoti M has received Abbvie, GSK, Gilead Sciences, Pfizer travel grants, speaker in own events; Lampertico P has served as Advisory Board/Speaker Bureau for Roche Pharma/Diagnostics, Gilead Sciences, GSK, AbbVie, Janssen, Myr, Eiger, Antios, Aligos, Vir, Grifols, Altona, Roboscreen; Coco B, Tosti ME, Ferrigno L, Brancaccio G, Ciancio A, Coppola C, Messina V, Claar E, Morisco F, Cacciola I, Pompili M, Russo FP, Izzi A, Niro GA, Coppola N, Alessandro F, Giulia M, Villa E, Gaeta GB and PITER Collaborating Investigators declare that they have no conflict of interest regarding this manuscript.

Data sharing statement: By protocol, the property of the data is of participating clinical centers while Istituto Superiore di Sanità acts as coordinating center for data management and analysis. Cumulative data are reported within the paper whereas each patient data is not fully available and without restrictions for ethical reasons. Dr. Kondili (loreta.kondili@iss.it) is in charge for data management and the readers may contact her for specific data request. She will provide the necessary ethical clearances for access to data.

STROBE statement: The authors have read the STROBE Statement—a checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-a checklist of items.

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REFERENCES

1 **1 Guy J**, Yee HF Jr. Health disparities in liver disease: Time to take notice and take action. *Hepatology* 2009; **50**: 309-313 [*RCA*] [PMID: 19554619 DOI: 10.1002/hep.22942] [FullText] [Full Text(PDF)]
2 **Mauvais-Jarvis F**, Bairey Merz N, Barnes PJ, Brinton RD, Carrero JJ, DeMeo DL, De Vries GJ, Epperson CN, Govindan R, Klein SL, Lonardo A, Maki PM, McCullough LD, Regitz-Zagrosek V, Regensteiner JG, Rubin JB, Sandberg K, Suzuki A. Sex and gender: modifiers of health, disease, and medicine. *Lancet* 2020; **396**: 565-582 [*RCA*] [PMID: 32828189 DOI: 10.1016/S0140-6736(20)31561-0] [FullText] [Full Text(PDF)]
3 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [*RCA*] [PMID: 33538338 DOI: 10.3322/caac.21660] [FullText]
4 **Wang SH**, Chen PJ, Yeh SH. Gender disparity in chronic hepatitis B: Mechanisms of sex hormones. *J Gastroenterol Hepatol* 2015; **30**: 1237-1245 [*RCA*] [PMID: 25708186 DOI: 10.1111/jgh.12934] [FullText]
5 **Brown R**, Goulder P, Matthews PC. Sexual Dimorphism in Chronic Hepatitis B Virus (HBV) Infection: Evidence to Inform Elimination Efforts. *Wellcome Open Res* 2022; **7**: 32 [*RCA*] [PMID: 36212217 DOI: 10.12688/wellcomeopenres.17601.3] [FullText] [Full Text(PDF)]
6 **Ma WL**, Lai HC, Yeh S, Cai X, Chang C. Androgen receptor roles in hepatocellular carcinoma, fatty liver, cirrhosis and hepatitis. *Endocr Relat Cancer* 2014; **21**: R165-R182 [*RCA*] [PMID: 24424503 DOI: 10.1530/ERC-13-0283] [FullText]
7 **Yu MW**, Chang HC, Chang SC, Liaw YF, Lin SM, Liu CJ, Lee SD, Lin CL, Chen PJ, Lin SC, Chen CJ. Role of reproductive factors in hepatocellular carcinoma: Impact on hepatitis B- and C-related risk. *Hepatology* 2003; **38**: 1393-1400 [*RCA*] [PMID: 14647050 DOI: 10.1016/j.hep.2003.09.041] [FullText]
8 **Villa E**, Karampatou A, Cammà C, Di Leo A, Luongo M, Ferrari A, Petta S, Losi L, Taliani G, Trande P, Lei B, Graziosi A, Bernabucci V, Critelli R, Pazienza P, Rendina M, Antonelli A, Francavilla A. Early menopause is associated with lack of response to antiviral therapy in women with chronic hepatitis C. *Gastroenterology* 2011; **140**: 818-829 [*RCA*] [PMID: 21167831 DOI: 10.1053/j.gastro.2010.12.027] [Full Text]
9 **Kondili LA**, Brancaccio G, Tosti ME, Coco B, Quaranta MG, Messina V, Ciancio A, Morisco F, Cossiga V, Claar E, Rosato V, Ciarallo M, Cacciola I, Ponziani FR, Cerrito L, Coppola R, Longobardi F, Biliotti E, Rianda A, Barbaro F, Coppola N, Stanzione M, Barchiesi F, Fagiuoli S, Viganò M, Massari M, Russo FP, Ferrarese A, Laccabue D, Di Marco V, Blanc P, Marrone A, Morsica G, Federico A, Ieluzzi D, Rocco A, Foschi FG, Soria A, Maida I, Chessa L, Milella M, Rosselli Del Turco E, Madonia S, Chemello L, Gentile I, Toniutto P, Bassetti M, Surace L, Baiocchi L, Pellicelli A, De Santis A, Puoti M, Degasperi E, Niro GA, Zignego AL, Craxi A, Raimondo G, Santantonio TA, Brunetto MR, Gaeta GB; PITER Collaborating Investigators. A holistic evaluation of patients with chronic Hepatitis D virus (HDV) infection enrolled in the Italian PITER-B and delta cohort. *Int J Infect Dis* 2024; **146**: 107115 [*RCA*] [PMID: 38801968 DOI: 10.1016/j.ijid.2024.107115] [FullText]
10 **Rizzetto M**. The delta agent. *Hepatology* 1983; **3**: 729-737 [*RCA*] [PMID: 6413350 DOI: 10.1002/hep.1840030518] [FullText]
11 **Durand F**, Valla D. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. *J Hepatol* 2005; **42** Suppl: S100-S107 [*RCA*] [PMID: 15777564 DOI: 10.1016/j.jhep.2004.11.015] [FullText]
12 **Elias S**, Masad B, Nimer A. Serum Biomarkers for Evaluating Portal Hypertension. In: Patel VB, Preedy VR editors. Biomarkers in Disease: Methods, Discoveries and Applications. Germany: Springer, Dordrecht, 2016: 153-166
13 **Gotlieb N**, Schwartz N, Zelber-Sagi S, Chodick G, Shalev V, Shibolet O. Longitudinal decrease in platelet counts as a surrogate marker of liver fibrosis. *World J Gastroenterol* 2020; **26**: 5849-5862 [*RCA*] [PMID: 33132639 DOI: 10.3748/wjg.v26.i38.5849] [FullText] [Full Text (PDF)]
14 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines on hepatitis delta virus. *J Hepatol* 2023; **79**: 433-460 [*RCA*] [PMID: 37364791 DOI: 10.1016/j.jhep.2023.05.001] [FullText]
15 **European Association for the Study of the Liver (EASL)**; European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol* 2024; **81**: 492-542 [*RCA*] [PMID: 38851997 DOI: 10.1016/j.jhep.2024.04.031] [FullText]
16 **Austin PC**. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res* 2011; **46**: 399-424 [*RCA*] [PMID: 21818162 DOI: 10.1080/00273171.2011.568786] [FullText] [Full Text(PDF)]
17 **Robins JM**, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000; **11**: 550-560 [*RCA*] [PMID: 10955408 DOI: 10.1097/00001648-200009000-00011] [FullText]
18 **Stockdale AJ**, Kreuels B, Henrion MYR, Giorgi E, Kyomuhangi I, de Martel C, Hutin Y, Geretti AM. The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis. *J Hepatol* 2020; **73**: 523-532 [*RCA*] [PMID: 32335166 DOI: 10.1016/j.jhep.2020.04.008] [FullText] [Full Text(PDF)]
19 **Iacob S**, Gheorghe L, Onica M, Huiban L, Pop CS, Brisc C, Sirli R, Ester C, Brisc CM, Diaconu S, Rogoveanu I, Sandulescu L, Vuletici D, Trifan A. Prospective study of hepatitis B and D epidemiology and risk factors in Romania: A 10-year update. *World J Hepatol* 2024; **16**: 640-649 [*RCA*] [PMID: 38689751 DOI: 10.4254/wjh.v16.i4.640] [FullText] [Full Text(PDF)]
20 **Zi J**, Li YH, Wang XM, Xu HQ, Liu WH, Cui JY, Niu JQ, Chi XM. Hepatitis D virus dual-infection among Chinese hepatitis B patient related to hepatitis B surface antigen, hepatitis B virus DNA and age. *World J Gastroenterol* 2023; **29**: 5395-5405 [*RCA*] [PMID: 37900584 DOI: 10.3748/wjg.v29.i38.5395] [FullText] [Full Text(PDF)]
21 **Pisaturo M**, Alessio L, Di Fraia A, Macera M, Minichini C, Cordua E, Onorato L, Scotto G, Di Caprio G, Calò F, Sagnelli C, Coppola N. Hepatitis D virus infection in a large cohort of immigrants in southern Italy: a multicenter, prospective study. *Infection* 2022; **50**: 1565-1572 [*RCA*] [PMID: 36222979 DOI: 10.1007/s15010-022-01938-0] [FullText] [Full Text(PDF)]
22 **Palom A**, Rodríguez-Tajes S, Navascués CA, García-Samaniego J, Riveiro-Barciela M, Lens S, Rodríguez M, Esteban R, Buti M. Long-term

clinical outcomes in patients with chronic hepatitis delta: the role of persistent viraemia. *Aliment Pharmacol Ther* 2020; **51**: 158-166 [*RCA*] [PMID: 31721254 DOI: 10.1111/apt.15521] [FullText]

23 **Palom A**, Sopena S, Riveiro-Barciela M, Carvalho-Gomes A, Madejón A, Rodriguez-Tajes S, Roade L, García-Eliz M, García-Samaniego J, Lens S, Berenguer-Hayme M, Rodríguez-Frías F, Hernandez-Évole H, Isabel Gil-García A, Barreira A, Esteban R, Buti M. One-quarter of chronic hepatitis D patients reach HDV-RNA decline or undetectability during the natural course of the disease. *Aliment Pharmacol Ther* 2021; **54**: 462-469 [*RCA*] [PMID: 34181772 DOI: 10.1111/apt.16485] [FullText]

24 **Kamal H**, Westman G, Falconer K, Duberg AS, Weiland O, Haverinen S, Wejstål R, Carlsson T, Kampmann C, Larsson SB, Björkman P, Nystedt A, Cardell K, Svensson S, Stenmark S, Wedemeyer H, Aleman S. Long-Term Study of Hepatitis Delta Virus Infection at Secondary Care Centers: The Impact of Viremia on Liver-Related Outcomes. *Hepatology* 2020; **72**: 1177-1190 [*RCA*] [PMID: 32145073 DOI: 10.1002/hep.31214] [FullText]

25 **Rodríguez-Tajes S**, Palom A, Giráldez-Gallego Á, Moreno A, Urquijo JJ, Rodríguez M, Alvarez-Argüelles M, Diago M, García-Eliz M, Fuentes J, Martínez-Sapiña AM, Castillo P, Casado M, Pérez-Campos E, Muñoz R, Hernández-Conde M, Morillas RM, Granados R, Miquel M, Morillas MJ, García-Retortillo M, Carrión JA, Moreno JM, Montón C, González-Santiago JM, Lorente S, Cabezas J, Mateos B, Vázquez-Rodríguez S, Díaz-Fontenla F, Pinazo JM, Delgado M, Pérez-Palacios D, Horta D, Fernández-Marcos C, López C, Calleja JL, Fernández I, García-Samaniego J, Forns X, Buti M, Lens S. Characterizing Hepatitis Delta in Spain and the gaps in its management. *Gastroenterol Hepatol* 2025; **48**: 502222 [*RCA*] [PMID: 38908682 DOI: 10.1016/j.gastrohep.2024.502222] [FullText]

26 **Rizzetto M**, Canese MG, Aricò S, Crivelli O, Trepo C, Bonino F, Verme G. Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers. *Gut* 1977; **18**: 997-1003 [*RCA*] [PMID: 75123 DOI: 10.1136/gut.18.12.997] [FullText]

27 **Romeo R**, Foglieni B, Casazza G, Spreafico M, Colombo M, Prati D. High serum levels of HDV RNA are predictors of cirrhosis and liver cancer in patients with chronic hepatitis delta. *PLoS One* 2014; **9**: e92062 [*RCA*] [PMID: 24658127 DOI: 10.1371/journal.pone.0092062] [Full Text] [Full Text(PDF)]

28 **Schaper M**, Rodriguez-Frias F, Jardi R, Tabernero D, Homs M, Ruiz G, Quer J, Esteban R, Buti M. Quantitative longitudinal evaluations of hepatitis delta virus RNA and hepatitis B virus DNA shows a dynamic, complex replicative profile in chronic hepatitis B and D. *J Hepatol* 2010; **52**: 658-664 [*RCA*] [PMID: 20346531 DOI: 10.1016/j.jhep.2009.10.036] [FullText]

29 **Wedemeyer H**. Re-emerging interest in hepatitis delta: new insights into the dynamic interplay between HBV and HDV. *J Hepatol* 2010; **52**: 627-629 [*RCA*] [PMID: 20334947 DOI: 10.1016/j.jhep.2010.02.001] [FullText]

30 **Papatheodoridis G**, Mimidis K, Manolakopoulos S, Triantos C, Vlachogiannakos I, Veretanos C, Deutsch M, Karatapanis S, Goulis I, Elefsiniotis I, Cholongitas E, Sevastianos V, Christodoulou D, Samonakis D, Manesis E, Kapatais A, Papadopoulos N, Ioannidou P, Germanidis G, Giannoulis G, Lakiotaki D, Kogias D, Kranidioti H, Zisimopoulos K, Mela M, Kontos G, Fytili P, Manolaka C, Agorastou P, Pantzios SI, Papatheodoridi M, Karagiannakis D, Geladari E, Psychos N, Zachou K, Chalkidou A, Spanoudaki A, Thomopoulos K, Dalekos G. HERACLIS-HDV cohort for the factors of underdiagnosis and prevalence of hepatitis D virus infection in HBsAg-positive patients. *Liver Int* 2023; **43**: 1879-1889 [*RCA*] [PMID: 37288712 DOI: 10.1111/liv.15638] [FullText]

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