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Trends in chronic hepatitis B virus infection in Italy over a 10-year period: Clues from the nationwide PITER and MASTER cohorts toward elimination

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ABSTRACT

Objectives: The study measures trends in the profile of patients with chronic hepatitis B virus linked to care in Italy.

Methods: A cross-sectional, multicenter, observational cohort (PITER cohort) of consecutive patients with hepatitis B surface antigen (HBsAg) over the period 2019-2021 from 46 centers was evaluated. The reference was the MASTER cohort collected over the years 2012-2015. Standard statistical methods were used.

Results: The PITER cohort enrolled 4583 patients, of whom 21.8% were non-Italian natives. Compared with those in MASTER, the patients were older and more often female. The prevalence of hepatitis B e antigen (HBeAg) declined (7.2% vs 12.3; P <0.0001) and that of anti-hepatitis D virus (HDV) remained stable (9.3% vs 8.3%). In both cohorts, about 25% of the patients had cirrhosis, and those in the PITER cohort were older. HBeAg-positive was 5.0% vs 12.6% (P <0.0001) and anti-HDV positive 24.8% vs 17.5% (P <0.0017). In the logistic model, the variables associated with cirrhosis were anti-HDV-positive (odds ratio = 10.08; confidence interval 7.63-13.43), age, sex, and body mass index; the likelihood of cirrhosis was reduced by 40% in the PITER cohort. Among non-Italians, 12.3% were HBeAg-positive (vs 23.4% in the MASTER cohort; P <0.0001), and 12.3% were anti-HDV-positive (vs 11.1%). Overall, the adherence to the European Association for the Study of the Liver recommendations for antiviral treatment increased over time.

Conclusion: Chronic hepatitis B virus infection appears to be in the process of becoming under control in Italy; however, HDV infection is still a health concern in patients with cirrhosis and in migrants.

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Introduction

Hepatitis B virus (HBV) infection still accounts for an estimated 800,000 deaths worldwide, despite vaccination campaigns, which have been implemented in the majority of countries [1]. In January 2020, Italy became the first validated country in the European Region to have achieved regional hepatitis B control targets [2]. This reflects the impact of the compulsory national HBV vaccination program started in Italy in 1991, initially including all newborns and children aged 12 years (the latter for a period of 12 years) and then continued for all newborns [3]. As a consequence, at present, the population aged less than 40 years is protected by the vaccine, whereas chronic HBV infection still imposes an important clinical burden on the older population. Importantly, the prevalence of chronic hepatitis B surface antigen (HBsAg) carriers in the general population decreased from nearly 3% in the 1980s to an estimated less than 0.6% in the current year [4–6].

In the last 2 decades, Italy has been the site of an increasing immigration flow; at present, persons born abroad account for about 8.4% of the resident population [7,8], and attention to immigrants from geographical areas of high or moderate endemicity levels for HBV infection has increased. Indeed, among patients with chronic HBV infection, the proportion of non-Italian natives grew from 7% in the years 2006-2007 to 27% in 2012-2015 [9–11]. The high proportion of immigrants who are HBsAg carriers ± hepatitis D virus (HDV)/hepatitis C virus (HCV) co-infection or not vaccinated for HBV could not change the overall epidemiological profile of HBV infection in Italian natives; however, it could impact on the clinical burden of HBV and the need to care for individuals who are infected. On the other hand, during the last decade, the use of antivirals, such as tenofovir and entecavir, has been widely recommended [12], which has positively impacted the natural history of HBV infection.

Altogether, the factors mentioned previously have the potential to cause a rapid evolution in the profile of HBV infection and disease. In the current study, we aimed to cross-sectionally evaluate the clinical burden and to characterize the different phases of chronic HBV liver disease in health care centers in Italy based on the patients enrolled in the multicenter PITER HBV/HDV cohort. In addition, the updated data were compared with those obtained by the MASTER study conducted by the Italian Association for the Study of the Liver (AISF) during 2012-2015 [11]. The final aim was to contribute to the measurement of the achievement of the targets for HBV elimination defined by the World Health Organization.

Patients and methods

PITER is a structured network that benefits from an integrated collaboration involving Italy's National Institute of Public Health (Istituto Superiore di Sanità), the AISF, and the Italian Society for Infectious Diseases and their affiliated clinical centers [13]. The cohort enrolled consecutive patients who were HBsAg-positive who were seen in 46 infectious disease or gastroenterology/hepatology clinical centers from October 1, 2019; for the purpose of the current study, the database was frozen on December 31, 2021; the participating centers were well distributed over Italy (Supplementary Figure 1).

The inclusion criteria were consecutive patients with HBsAg positivity for at least 6 months with or without co-infection with HDV and/or HCV, independent of antiviral treatment. The exclusion criteria were patients with previous HBV infection who were HBsAg-negative at enrollment, patients with acute HBV hepatitis, and, for the purpose of the current study, patients with HIV co-infection. The virological and routine analyses were performed at each participating center using standard commercial kits.

For patients who were under antiviral treatment at the time of enrollment, the infection/disease stage was classified by each center, as recommended by the European Association for the Study of the Liver (EASL) clinical practice guidelines [12].

Liver cirrhosis was assessed either by liver biopsy (Metavir or Ishak score) or by transient elastography using a stiffness value equal to or higher than 12.5 kPa as the cut-off or by biochemical, image, and instrumental data. Specifically, the presence of esophageal or gastric varices and/or platelet count lower than 120,000/µl were considered indicative of cirrhosis. Liver stiffness measurements were considered valid if each patient had at least 10 stiffness measurements, with a success rate of at least 80%, an

Table 1
Main characteristics of the patients at enrollment.

Variables Median (Q1, Q3) or n (%)	PITER n = 4583	MASTER n = 2920	*P*-value
Age (years)	58.80 (47.92-68.22)	49.83 (38.59-60.25)	<0.0001
Sex (male)	2850 (62.27)	2003 (68.60)	<0.0001
Body mass index Missing 20.0%	24.14 (22.07-26.70)	23.83 (21.91-26.22)	0.0049
Body mass index ≥30	472 (13.18)	272 (11.24)	0.0248
Origin			<0.0001
Italian natives	3419 (78.20)	2136 (73.25)	
East Europe	547 (12.51)	386 (13.24)	
Africa	162 (3.71)	173 (5.93)	
Asia	221 (5.05)	194 (6.65)	
South and Central America	13 (0.30)	15 (0.51)	
Central Western Europe	10 (0.23)	12 (0.41)	
Alcohol use Missing 11.6%	1408 (34.21)	783 (31.13)	0.0098
Hepatitis B e antigen Missing 5.2%	322 (7.17)	323 (12.31)	<0.0001
Hepatitis B virus-DNA IU/ml Missing 6.1%			<0.0001
0	2629 (61.25)	958 (34.81)	
(0, 2000)	1115 (25.98)	691 (25.11)	
(>2000, 20000)	277 (6.45)	355 (12.90)	
>20000	271 (6.31)	748 (27.18)	
Cirrhosis	1107 (24.15)	722 (24.75)	0.5572
Anti-hepatitis D virus Missing 29.1%	314 (9.28)	161 (8.31)	0.2329
Anti-hepatitis C virus Missing 21.7%	169 (4.56)	81 (3.73)	0.1283
Hepatocellular carcinoma	210 (4.64)	110 (3.80)	0.0827
Previous therapy (mainly interferon based)	1354 (31.84)	983 (33.66)	0.1046
Ongoing therapy	3043 (66.56)	1000 (34.25)	<0.0001

Missing data were reported when >5%. Differences in missing data between the two cohorts ranged from 3.6 to 8.3%, except for anti-HDV which was not tested in 26.1% in the PITER cohort versus 33.6% in the MASTER cohort (P <0.0001).

interquartile range of less than 30% of the median stiffness score, and a body mass index (BMI) of <30 kg/m^2 [14]. Current alcohol abuse was defined as drinking more than three alcohol units per day [15].

The single patient data were collected using a specific electronic case report form. The data quality was checked through periodic remote monitoring using specific queries. Two expert clinical monitors and one physician were involved in ensuring data quality [13].

The data from the current cohort were compared with those of the multicenter Italian MASTER-B cohort, which enrolled patients using a similar enrollment and exclusion criteria, as previously reported [11]. Briefly, this was an independent AISF-endorsed study, which enrolled patients who were HBsAg-positive in 73 Italian centers from 2012 to the first quarter of 2015. The participating centers covered the entire country (Supplementary Figure 1); there was no difference from the PITER cohort as to the type of center (gastroenterology/infectious diseases/internal medicine). In both studies, the physicians at each center established the patient's HBV treatment regimen according to the current clinical practice guidelines.

For the aim of the present study, a unique dBase was prepared, codifying equally the variables present in both cohorts.

Statistical analysis

Continuous variables were described by the median and first and third quartiles; categorical variables were described by absolute frequencies and percentages. To compare the groups, we used the chi-square test for categorical variables (Fisher's exact test was preferred in the case of sparse tables) and Student's *t*-test for continuous variables (or Wilcoxon rank-sum test when a significant departure from normality was detected).

A multivariable analysis was undertaken using logistic regression. The odds ratio (OR) estimates were obtained by the method of maximum likelihood; 95% confidence intervals (CIs) were based on the profile likelihood. For the continuous predictors, linearity was assessed by plots of deviance residuals versus covariate values. The significance of the estimated effects was tested using the Wald chi-square statistic.

The statistical analyses were performed using the SAS statistical package, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

The PITER study enrolled 4583 patients with plasma positivity for HBsAg, who were observed throughout Italy from October 1, 2019 to December 31, 2021. The main patient characteristics were compared with those recorded in the MASTER-B cohort, which enrolled 2920 patients who were HBsAg-positive from June 1, 2012 to the end of enrollment on March 30, 2015 (Table 1). Overall, the patients in the PITER cohort were older (median age difference + 8.97 years): 21.8% of them were aged ≤40 years versus 28% in the MASTER cohort. The proportion of Italian patients aged <40 years decreased from 14.6% in the MASTER to 3.8% in the PITER study. In addition, the most recent cohort showed a greater proportion of females and a lower percentage of non-Italian natives (21.8% vs 26.8%), the majority (76.3%) of whom had been in Italy for more than 10 years. The proportion of patients who tested positive for hepatitis B e antigen (HBeAg) decreased sharply (7.2% vs 12.3%) from the MASTER to the PITER cohort; the majority of the cases in the PITER cohort had an undetectable serum HBV DNA, which mirrors the increased percentage of subjects under antiviral therapy compared with the MASTER cohort. Anti-HDV antibodies were present in 9.3% versus 8.3% in the MASTER co-

Table 2
Characteristics of the patients with cirrhosis in the two study cohorts.

Variables Median (Q1, Q3) or n (%)	PITER Cirrhosis n = 1107 (24.15)	MASTER Cirrhosis n = 722 (24.75)	*P*-value
Age (years)	63.63 (55.58, 71.89)	57.23 (47.68, 65.52)	<0.0001
Sex (males)	816 (73.91)	577 (79.92)	0.0032
Body mass index	25.59 (23.18, 28.34)	25.59 (23.45, 27.92)	0.9063
Body mass index ≥ 30	127 (15.34)	92 (15.11)	0.9040
Hepatitis B virus-DNA (positive)	257 (24.66)	392 (56.57)	<0.0001
Origin			<0.0001
Italian natives	896 (86.40)	578 (80.06)	
East Europe	89 (8.58)	56 (7.76)	
Asia	31 (2.99)	43 (5.96)	
Africa	19 (1.83)	42 (5.82)	
South and Central America	1 (0.10)	3 (0.42)	
Central Western Europe	1 (0.10)	0 (0.00)	
Alcohol use (yes)	366 (37.16)	187 (29.78)	0.0023
Hepatitis B e antigen (positive)	54 (4.97)	81 (12.64)	<0.0001
Anti-hepatitis D virus (positive)	213 (24.80)	88 (17.50)	0.0017
Anti-hepatitis C virus (positive)	71 (7.85)	35 (6.06)	0.1900
Hepatocellular carcinoma (present)	183 (16.62)	99 (14.04)	0.1408
Previous therapy (yes)	402 (38.95)	278 (38.50)	0.8492
Ongoing therapy (yes)	1012 (91.58)	365 (50.55)	<0.0001

hort ($P = 0.2329$); of note, anti-HDV antibodies were not tested in 26.1% in the PITER cohort versus 33.6% in the MASTER cohort ($P < 0.0001$). No difference between the cohorts was observed in the prevalence of cirrhosis, hepatocellular carcinoma (HCC), and anti-HCV antibodies. Moreover, patients without cirrhosis (Supplementary Table 1) were significantly older in the PITER cohort (median age difference + 10.4 years) and less frequently male (58.6% vs 64.8%); about one-third of them reported alcohol use. Notably, the proportion of HBeAg-positive cases was 7.9% versus 12.2% in the MASTER study ($P < 0.0001$), and anti-HDV antibodies were detected in 4.0% versus 5.0% ($P = 0.1303$).

According to the EASL classification, patients in the PITER cohort were classified as 1.9% e+ infection, 5.6% e+ chronic hepatitis, 20.0% e- infection, and 72.5% e- chronic hepatitis; the corresponding percentages for the MASTER cohort were 0.6%, 11.6%, 18.9%, and 68.9%, respectively.

Cirrhosis

Patients with cirrhosis (Table 2) were older in the PITER cohort (median age difference + 6.4 years); 86.4% of the patients were Italians versus 80.1% in the MASTER cohort. The proportion of HBeAg-positive cases was 5.0% versus 12.6% in the past ($P < 0.0001$); by contrast, anti-HDV antibodies were detected in 24.8% of the cases versus 17.5% of those in the past ($P < 0.0017$); anti-HCV antibodies were present in 7.9% versus 6.1%, respectively, and HCC in 16.6% versus 14.0%.

The crude percentage of patients with cirrhosis was almost identical in the two study cohorts (24.8% vs 24.2%). A logistic model was fitted to compare the presence of cirrhosis in the two cohorts, taking their different features into account (Table 3). The presence of anti-HDV antibodies was by far the most significant factor (OR = 10.09; 95% CI = 7.63, 13.43). Other significant predictors were age, sex, and BMI; for age and BMI, residual analysis confirmed a linear effect. Notably, after the adjustment for significant predictors, the likelihood of cirrhosis in the PITER cohort was reduced by about 40% compared with the MASTER cohort (OR = 0.61; 95% CI = 0.51, 0.72); in addition, being non-Italian was associated with an increased risk of cirrhosis (OR = 1.56; 95% CI = 1.22, 1.99).

Non-Italian natives

As expected, within each cohort, non-Italian patients were younger and showed a higher prevalence of females, the positivity for HBeAg or anti-HDV was more frequent among immigrants, and the proportion of patients on treatment was lower among non-Italians (these comparisons are not shown). Interestingly, the profiles of the non-Italian patients showed remarkable changes between the two cohorts (Table 4); they were now older (median age difference + 6.4 years) and showed an increased prevalence of females, alcohol use became more frequent, the HBeAg prevalence was almost halved (12.2% vs 23.5%), whereas the prevalence of anti-HDV antibodies (12.3%) remained stable. Cirrhosis among foreigners was less frequent in the PITER cohort, whereas no difference was present in the prevalence of HCC. Similarly, the patients of Italian origin were older in the PITER cohort (median age difference + 7.7 years) and more frequently female than in the past; of note, the proportion of the patients positive for HBeAg declined (5.9% vs 8.2%; $P = 0.0014$). The prevalence of anti-HDV positivity remained almost stable (8.0% vs 7.3%), as did the proportion of patients with cirrhosis or HCC.

Adherence to treatment recommendations

We examined the patients who were not on treatment with nucleos(t)ide analogs (NUCs) at the time of enrollment in the PITER (n = 1456) and MASTER cohorts (n = 1860), categorized by HBV DNA concentration (Figure 1). Overall, only 5.6% in the PITER cohort with a HBV DNA >20,000 IU/ml were not under antiviral therapy; this percentage was 35.9% in the MASTER cohort. Among patients with cirrhosis, in the PITER cohort, 10.6% with an HDV DNA value >2000 did not receive treatment; in the MASTER cohort, the corresponding percentage was 62%.

Table 3
Factors associated to the likelihood of cirrhosis. Results from the fitted logistic models.

	Odds ratio	95% confidence interval	Wald χ^2 statistic	*P*-value
Cohort (PITER vs MASTER)	0.61	(0.51, 0.72)	31.77	<0.0001
Sex (Females vs males)	0.43	(0.35, 0.52)	77.27	<0.0001
Age (linear effect, × 5 year increment)	1.32	(1.27, 1.37)	210.43	<0.0001
Body mass index (linear effect, x unit increment)	1.03	(1.01, 1.05)	6.08	0.0137
Anti-hepatitis D virus (present vs absent)	10.09	(7.63, 13.43)	256.58	<0.0001
Hepatitis B e antigen (present vs absent)	1.15	(0.83, 1.58)	0.75	0.3857
Anti-hepatitis C virus (present vs absent)	1.40	(0.94, 2.08)	2.80	0.0944
Alcohol use (yes vs no)	0.91	(0.76, 1.08)	1.26	0.2608
Origin (Italian non-natives vs Italian natives)	1.56	(1.22, 1.99)	12.53	0.0004

Table 4
Characteristics of the patients enrolled in PITER and MASTER cohorts, by Italian and non-Italian origin.

Variables Median (Q1, Q3) or n (%)	Patients of non-Italian origin			Patients of Italian origin		
	PITER n = 953 (21.80)	MASTER n = 780 (26.75)	*P*-value	PITER n = 3419 (78.20)	MASTER n = 2136 (73.25)	*P*-value
Age (years)	41.66 (34.30, 49.90)	35.29 (28.65, 43.49)	<0.0001	62.27 (54.31, 70.37)	54.58 (44.75, 63.01)	<0.0001
Sex (Males)	496 (52.10)	453 (58.08)	0.0129	2223 (65.10)	1547 (72.43)	<0.0001
Body mass index	24.14 (22.07, 26.70)	23.83 (21.91, 26.22)	0.1322	25.47 (23.20, 28.09)	25.26 (23.12, 27.73)	0.0607
Body mass index ≥30	67 (8.82)	43 (7.14)	0.2605	397 (14.24)	228 (12.56)	0.1020
Hepatitis B virus-DNA (detectable)	503 (54.73)	585 (80.36)	<0.0001	1186 (35.99)	1252 (60.63)	<0.0001
Alcohol use	323 (35.57)	171 (26.39)	0.0001	1072 (33.97)	612 (32.78)	0.3891
Hepatitis B e antigen	114 (12.23)	166 (23.48)	<0.0001	198 (5.91)	157 (8.21)	0.0014
Anti-hepatitis D virus	94 (12.26)	59 (11.07)	0.5139	205 (7.96)	102 (7.27)	0.4372
Anti-hepatitis C virus	14 (1.71)	13 (2.28)	0.5542	151 (5.31)	68 (4.26)	0.1211
Cirrhosis	141 (14.80)	144 (18.46)	0.0405	896 (26.21)	578 (27.10)	0.4644
Hepatocellular carcinoma	12 (1.28)	9 (1.16)	0.9999	171 (5.06)	101 (4.77)	0.6291
Previous therapy	203 (22.48)	183 (23.46)	0.6331	1139 (34.49)	800 (37.45)	0.0261
Ongoing therapy	501 (52.57)	157 (20.13)	<0.0001	2397 (70.31)	843 (39.47)	<0.0001

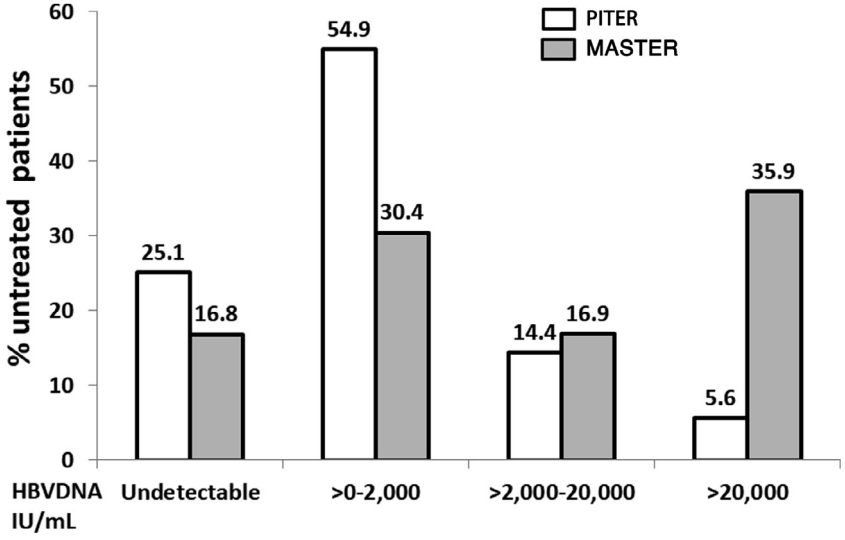

Figure 1. Distribution of untreated patients according to HBV DNA plasma concentrations.
HBV, hepatitis B virus.

Discussion

The rapid evolution of the clinical and epidemiological burden of HBV infection in Italy is primarily due to three factors: (i) the ongoing effect of systematic anti-HBV vaccination; (ii) the widespread use of antiviral drugs that block the progression of the liver disease and abolish the infectivity of patients, and (iii) immigration from areas where HBV is endemic.

The role of each factor and the modification of its weight over time appear clearly in the current study. As recalled from the Introduction section, the compulsory vaccination program has raised a barrier against HBV infection in younger Italian residents. In the PITER cohort, only 3.8% of Italian patients were aged below 40 years compared with 44.3% among foreigners. The small residual number of the Italian cases is consistent with the acceleration of the vaccination campaign during the first years [16] and corroborates the concept that the elimination of HBV infection is imminent among patients born in Italy; a further indicator of the reduction of new chronic infections is the dramatic reduction of HBeAg-positive cases compared with the period 2012-2015. Although their proportion remains the same as in the past cohort, the mean age of patients with cirrhosis is increasing as a consequence of the lack of renewal with new younger patients; we can expect a drop in the number of cirrhosis and then of HCC cases in the coming years,

at least among patients with HBV monoinfection. A further contribution to the reduction in the burden of advanced liver disease will come from the extended use of antiviral therapy, mainly NUCs, which can stop the progression of liver disease to advanced stages and even cause the regression of fibrosis in patients with cirrhosis [17,18]. In the PITER cohort, 66.6% of the patients were under therapy, which is a proportion almost double that of the MASTER cohort. It is reassuring that there was an increase over time in adherence to the treatment indication according to the EASL recommendations, as shown in Figure 1, with only 5.6% of the patients not being on treatment at the time of enrollment, despite an HBV DNA value >20,000 IU/ml; the corresponding percentage in the MASTER cohort was 35.6%, *i.e.*, more than six times higher.

The improvement in the treatment rate observed in the PITER cohort, other than the individual benefit discussed previously, may acquire the value of treatment as prevention at the community level. Indeed, abating viremia would be an effective means of stopping the transmission from young persons with a high level of plasma HBV DNA to susceptible individuals, which occurs mainly through sexual intercourse or within the family. To date, the role of treatment as prevention has been thoroughly assessed for persons with HIV who achieve optimal viral suppression while under therapy [19]. Because young persons with HBV are predominantly of non-Italian origin, once again, programs to reduce the barriers to access to therapy are needed.

Overall, co-infection with HDV was detected in 9.3% of study participants, with a higher prevalence among non-Italian natives. There was a positive trend compared with the MASTER study toward testing patients who were HBsAg-positive for anti-HDV; although, 26.1% of the patients remained untested. The availability of new therapies against HDV [20] should act as a potent incentive for screening. The presence of anti-HDV maintains a significant role as a driver of cirrhosis, being present in 24.8% of cirrhosis cases, a proportion higher than that in the MASTER study (17.5%). Clearly, the increase in this proportion might be influenced by the increase in testing; however, it seems likely that a relative increment in the proportion of HDV cases is due to the reduction of cirrhosis cases among patients with HBV monoinfection for the reasons discussed previously. Indeed, the prevalence of anti-HDV remained stable over time in the subset of patients of Italian origin, patients without cirrhosis, and patients of non-Italian origin. This interpretation is supported by the disproportionate role of HDV as the cause of decompensation and liver cancer leading to transplant in two Italian studies [21,22]. Similar findings were reported in two studies from Spain [23,24]. The major role of HDV infection in cirrhosis was confirmed by the logistic model, together with those of age, sex, and BMI. Interestingly, the model showed that being part of the PITER cohort, with other characteristics being equal, lowered the likelihood of cirrhosis by about 40% compared with the MASTER cohort. We can hypothesize that the patient management improved in the period between the two studies, particularly due to the increasing use of antivirals, whereas some patients died or underwent liver transplant. Similarly, when the confounders were controlled, non-Italian natives showed a high likelihood of cirrhosis. The prevalence of more aggressive HBV/HDV genotypes or subtypes, the acquisition of the infection at birth, or the exposure to environmental factors in their countries of origin are potential causes not explored by the current studies. In any case, the analysis suggests caution in interpreting the crude prevalence in clinical/epidemiological studies.

Non-Italian natives account for 22-27% of the patients in the current and in the MASTER cohort, respectively. Migrants were definitely younger than Italian patients in both cohorts but older in the current cohort than in the past one. The PITER study enrolled participants during the peaks of the COVID-19 epidemic, when there were restrictions on immigration flows and barriers to access to in- and out-patient clinics [25,26]; so, it is likely that new waves of younger patients diminished. Indeed, 76% of non-Italian natives were subjects who had been in Italy for more than 10 years. Because enrollment in the PITER study is ongoing, it would be interesting to monitor this aspect.

A further point is the increasing prevalence of females among non-Italian natives which, coupled with their young age, leads to a high number of women of childbearing age [27]. Screening pregnant women for HBV infection is a consolidated habit in public and private hospitals in Italy and should help in preventing mother-to-child transmission by adequate prophylaxis. However, the adherence to prophylaxis may be suboptimal among non-Italian women [28]; so, the continuity in the care of mothers and neonates should be pursued by offering dedicated assistance points, particularly in disadvantaged areas, which are sites of undocumented immigration. At present, there are around 5.5 million non-Italian natives officially residing in Italy, to which should be added an estimated 500,000 illegal residents or waiting for asylum [8], whose characteristics are not included in this study.

As usual, the study has some limitations and strengths. While its multicenter design allows a realistic view of the health status of the patients with HBV who are somehow linked to care, it may suffer from potential heterogeneity of methods and evaluations; regardless, the strict connections of the centers with the reference scientific societies might have counteracted this potential bias. The PITER and MASTER cohorts were enrolled using the same criteria, and the participating centers were distributed over the entire Italian territory, had the same specialization, and enrolled consecutive patients, which makes them representative of the Italian epidemiological burden in the two periods. The number of centers participating in PITER was smaller, and each enrolled a higher number of patients than the MASTER study; this could reflect the national policy in recent years of combining the regional centers allowed to prescribe antiviral therapies. In addition, in the same period, data were published that reinforced the concept that NUCs could reverse cirrhosis and avoid the progression of liver disease when given at an early stage [17,18]; these findings enhanced awareness among general practitioners and specialists and possibly caused a higher number of patients to be sent to specialist centers. A further limitation of the current data was that more detailed virological analyses remained outside the scope of the study.

In conclusion, the data depict a rapidly evolving scenario for HBV infection in Italy, mainly due to the progressive exhaustion of HBV infection among Italian natives and highlight new needs to meet health demands.

Declaration of Competing Interest

The authors have no competing interests to declare.

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Ethical approval

This study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008, and the principles of Good Clinical Practice. The protocol of the PITER study was approved by the Ethics Committee of the Istituto Superiore di Sanità ISS on 24th July 2019, and by the Ethics Committees of each participating institution that are listed in the PITER Collaborating Group available at www.iss.it/piter. All patients included in the database signed an informed consent prior to enrolment. The patients' data were evalu-

ated through an anonymous analysis, adopting codes generated by the electronic case-report form. The MASTER study followed similar ethic procedures.

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Authors' contribution

GB: Investigation, Resources, Writing – original draft, Visualization, Writing – review & editing. BC: Investigation, Resources, Writing – original draft, Writing – review & editing. AN: Investigation, Methodology, Validation, Formal analysis, Data curation, Writing – review & editing. MGQ: Resources, Visualization, Writing – review & editing. MET: Investigation, Formal analysis, Data curation. LF: Data curation. IC, VM, LC, FM, MM, FB, ACi, FPR, NC, PB, EC, GV, MP, ALZ, LC, RSM, SF, AM, CF, PL, VDM, ACr, TAS, GR: Resources, Writing – review & editing. MRB: Investigation, Resources, Writing – review & editing. GBG: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. LAK: Conceptualization, Supervision, Funding acquisition, Writing – original draft, Writing – review & editing. PITER Collaborating Investigators contributed to data collection and data quality check. All authors approved the final version of the manuscript.

Appendix A

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.02.006.

References

[1] World Health Organization. Hepatitis B, https://www.who.int/news-room/fact-sheets/detail/hepatitis-b; 2022 [accessed 03 February 2023].
[2] Khetsuriani N, Mosina L, Van Damme P, Mozalevskis A, Datta S, Tohme RA. Progress toward hepatitis B control - World Health Organization European region, 2016–2019. *MMWR Morb Mortal Wkly Rep* 2021;**70**:1029–35. doi:10.15585/mmwr.mm7030a1.
[3] Stroffolini T. The changing pattern of hepatitis B virus infection over the past three decades in Italy. *Dig Liver Dis* 2005;**37**:622–7. doi:10.1016/j.dld.2005.02.010.
[4] Pasquini P, Kahn HA, Pileggi D, Panà A, Terzi J, Guzzanti E. Prevalence of hepatitis B markers in Italy. *Am J Epidemiol* 1983;**118**:699–709. doi:10.1093/oxfordjournals.aje.a113680.
[5] Giusti G, Galanti B, Gaeta GB, Piccinino F, Ruggiero G. HBsAg carriers among blood donors in Italy; a retrospective survey of data from 189 blood banks. *Hepatogastroenterology* 1981;**28**:96–8.
[6] Polaris Observatory CollaboratorsGlobal prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol* 2018;**3**:383–403. doi:10.1016/S2468-1253(18)30056-6.
[7] Istituto Nazionale di Statistica. Indicatori demografici. Italy: Istituto Nazionale di Statistica; 2020. https://www.istat.it/it/files/2021/05/REPORT_INDICATORI-DEMOGRAFICI-2020.pdf [accessed 03 Febraury 2023].
[8] Fondazione Migrantes. Caritas e migrantes. XXX Rapporto Immigrazione 2021. Verso un noi sempre più grande, https://www.migrantes.it/xxx-rapporto-immigrazione-2021-verso-un-noi-sempre-piu-grande/; 2021 [accessed 03 February 2023].
[9] Stroffolini T, Almasio PL, Sagnelli E, Mele A, Gaeta GBItalian Hospitals' Collaborating Group. Evolving clinical landscape of chronic hepatitis B: a multicenter Italian study. *J Med Virol* 2009;**81**:1999–2006. doi:10.1002/jmv.21643.

[10] Fasano M, Saracino A, Carosi G, Mazzotta F, Marino N, Sagnelli E, et al. Hepatitis B and immigrants: a SIMIT multicenter cross-sectional study. *Infection* 2013;**41**:53–9. doi:10.1007/s15010-012-0384-9.
[11] Brancaccio G, Nardi A, Madonia S, Fasano M, Verucchi G, Massari M, et al. The present profile of chronic hepatitis B virus infection highlights future challenges: an analysis of the Multicenter Italian Master-B cohort. *Dig Liver Dis* 2019;**51**:438–42. doi:10.1016/j.dld.2018.09.008.
[12] European Association for the Study of the LiverElectronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017;**67**:370–98. doi:10.1016/j.jhep.2017.03.021.
[13] Kondili LA, Vella SPITER Collaborating Group. PITER: an ongoing nationwide study on the real-life impact of direct acting antiviral based treatment for chronic hepatitis C in Italy. *Dig Liver Dis* 2015;**47**:741–3. doi:10.1016/j.dld.2015.05.022.
[14] Li Y, Huang YS, Wang ZZ, Yang ZR, Sun F, Zhan SY, et al. Systematic review with meta-analysis: the diagnostic accuracy of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B. *Aliment Pharmacol Ther* 2016;**43**:458–69. doi:10.1111/apt.13488.
[15] Dawson DA, Grant BF, Li TK. Quantifying the risks associated with exceeding recommended drinking limits. *Alcohol Clin Exp Res* 2005;**29**:902–8. doi:10.1097/01.alc.0000164544.45746.a7.
[16] Stroffolini T, Cialdea L, Tosti ME, Grandolfo M, Mele A. Vaccination campaign against hepatitis B for 12-year-old subjects in Italy. *Vaccine* 1997;**15**:583–5. doi:10.1016/s0264-410x(96)00197-1.
[17] Asselah T, Marcellin P. Long-term results of treatment with nucleoside and nucleotide analogues (entecavir and tenofovir) for chronic hepatitis B. *Clin Liver Dis* 2013;**17**:445–50. doi:10.1016/j.cld.2013.05.001.
[18] Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet* 2013;**381**:468–75. doi:10.1016/S0140-6736(12)61425-1.
[19] Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med* 2016;**375**:830–9. doi:10.1056/NEJMoa1600693.
[20] Degasperi E, Anolli MP, Lampertico P. Bulevirtide for patients with compensated chronic hepatitis delta: a review. *Liver Int* 2022. doi:10.1111/liv.15389.
[21] Brancaccio G, Vitale A, Signoriello G, Gaeta GB, Cillo U. Changing indications for liver transplant: slow decline of hepatitis viruses in Italy. *Infect Dis (Lond)* 2020;**52**:557–62. doi:10.1080/23744235.2020.1763453.
[22] Caviglia GP, Martini S, Ciancio A, Niro GA, Olivero A, Fontana R, et al. The hepatitis D virus in Italy. A vanishing infection, not yet a vanished disease. *J Adv Res* 2021;**33**:183–7. doi:10.1016/j.jare.2021.02.009.
[23] Ramos-Rincon J-M, Pinargote H, Ramos-Belinchón C, de Mendoza C, Aguilera A, Soriano V. Hepatitis delta in patients hospitalized in Spain (1997–2018). *AIDS* 2021;**35**:2311–18. doi:10.1097/QAD.0000000000003024.
[24] Ramos-Rincon JM, Pinargote-Celorio H, de Mendoza C, Ramos-Belinchón C, Barreiro P, Treviño A, et al. Impact of potent nucleos(t)ide therapy on hepatitis B hospitalisations in Spain. *Aliment Pharmacol Ther* 2022. doi:10.1111/apt.17280.
[25] Aghemo A, Masarone M, Montagnese S, Petta S, Ponziani FR, Russo FP, et al. Assessing the impact of COVID-19 on the management of patients with liver diseases: a national survey by the Italian association for the study of the Liver. *Dig Liver Dis* 2020;**52**:937–41. doi:10.1016/j.dld.2020.07.008.
[26] Kondili LA, Buti M, Riveiro-Barciela M, Maticic M, Negro F, Berg T, et al. Impact of the COVID-19 pandemic on hepatitis B and C elimination: an EASL survey. *JHEP Rep* 2022;**4**:100531. doi:10.1016/j.jhepr.2022.100531.
[27] Lembo T, Saffioti F, Chiofalo B, Granese R, Filomia R, Grasso R, et al. Low prevalence of hepatitis B and hepatitis C virus serum markers in a cohort of pregnant women from Southern Italy. *Dig Liver Dis* 2017;**49**:1368–72. doi:10.1016/j.dld.2017.07.012.
[28] Spada E, Mele A, Ciccozzi M, Tosti ME, Bianco E, Szklo A, et al. Changing epidemiology of parenterally transmitted viral hepatitis: results from the hepatitis surveillance system in Italy. *Dig Liver Dis* 2001;**33**:778–84. doi:10.1016/s1590-8658(01)80695-2.