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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 towards elimination

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Abstract

Objectives. The study measures trends in the profile of patients with chronic HBV linked to care in Italy.

Methods. Cross sectional, multicentre, observational cohort (PITER cohort) of consecutive HBsAg-positive patients over the period 2019–2021 in 46 centres. 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 to those in MASTER, the patients were older and more often female. The prevalence of HBeAg declined (7.2% vs 12.3; $p < 0.0001$), and that of anti-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+ was 5.0% vs 12.6% ($p < 0.0001$) and anti-HDV+ 24.8% vs 17.5% ($p < 0.0017$). In the logistic model, the variables associated with cirrhosis were anti-HDV+ (OR = 10.08; C.I. 7.63–13.43) age, gender and BMI; 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 adherence to EASL recommendations for antiviral treatment increased over time.

Conclusions. Chronic HBV infection appears to be in process of becoming under control; HDV infection is still a health concern in patients with cirrhosis and in migrants.

Keywords: Hepatitis B, chronic; Hepatitis Delta; Epidemiology; Migrants; Hepatitis control

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 new-borns plus 12-year-old children (the latter for a period of 12 years) and then continued for all new-borns [3]. As a consequence, at present, the population less than 40 years old is protected by the vaccine, while chronic HBV infection still imposes an important clinical burden in the older population. Importantly, the prevalence of chronic HBsAg carriers in the general population decreased from nearly 3% in the 1980s to an estimated less than 0.6% in current year [4–6].

In the last two 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 ±HDV/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 infected individuals. 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 on the natural history of HBV infection.

Altogether, the factors mentioned above have the potential to cause a rapid evolution in the profile of HBV infection and disease. In the present study, we aimed to cross-sectionally evaluate the clinical burden and to characterise the different phases of chronic HBV liver disease in health care centres in Italy based on the patients enrolled in the multicentre 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 is to contribute to 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 (SIMIT) and their affiliated clinical centres [13]. The cohort enrolled consecutive HBsAg-positive patients seen in 46 infectious disease or gastroenterology/hepatology clinical centres from November 2019; for the purpose of the present study, the database was frozen on 31 December 2021; the participating centres 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, independently of antiviral treatment. The exclusion criteria were patients with previous HBV infection who were HBsAg negative at enrolment, acute HBV hepatitis and, for the purpose of the present study, patients with HIV co-infection. The virological and routine analyses were performed at each participating centre using standard commercial kits.

For patients who were under antiviral treatment at the time of enrolment, the infection/disease stage was classified by each centre as recommended by the EASL clinical practice guidelines[12].

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

measurements, with a success rate of at least 80%, an 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/day [15].

The single patient data were collected using a specific electronic Case Report Form (eCRF). 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 present cohort were compared with those of the multicentre, Italian MASTER-B cohort, which enrolled patients using similar enrolment and exclusion criteria, as previously reported [11]. Briefly, this was an independent AISF-endorsed study, which enrolled HBsAg-positive patients in 73 Italian centres over the period from 2012 to the first quarter of 2015. The participating centres covered the entire country (Supplementary Figure1); there was no difference from the PITER cohort as to the type of centre (gastroenterology/infectious diseases/internal medicine). In both studies, the physicians at each centre 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 groups, we used the χ^2 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).

Multivariable analysis was undertaken using logistic regression. Odds ratio estimates were obtained by the method of maximum likelihood; 95% confidence intervals were based on the profile

likelihood. For continuous predictors, linearity was assessed by plots of deviance residuals vs covariate values. The significance of the estimated effects was tested using the Wald χ^2 statistic. 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, observed throughout Italy in the period from 1 October 2019 to 31 December 2021. The main patient characteristics were compared with those recorded in the MASTER-B cohort, which enrolled 2920 HBsAg-positive patients from 1 June 2012 to the end of enrolment on 30 March 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 vs 28% in the MASTER cohort. The proportion of Italian patients below age 40 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 of whom (76.3%) had been in Italy for more than 10 years. The proportion of HBeAg-positive patients decreased sharply (7.2% vs 12.3%) from the MASTER to the PITER cohort; the majority of the cases in the PITER cohort had undetectable serum HBV DNA, which mirrors the increased percentage of subjects under antiviral therapy as compared to the MASTER cohort. Anti-HDV antibodies were present in 9.3% vs 8.3% in the MASTER cohort ($p = 0.2329$); of note, anti-HDV antibodies were absent in 26.1% in the PITER cohort vs 33.6% in the MASTER cohort ($p < 0.0001$). No difference between the cohorts was observed in the prevalence of cirrhosis, 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% vs 12.2% in the MASTER study ($p < 0.0001$), and anti-HDV antibodies were detected in 4.0% vs 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 vs 80.1% in the MASTER cohort. The proportion of HBeAg-positive cases was 5.0% vs 12.6% in the past ($p < 0.0001$); by contrast, anti-HDV antibodies were detected in 24.8% of the cases vs 17.5% of those in the past ($p < 0.0017$); anti-HCV antibodies were present in 7.9% vs 6.1%, respectively, and HCC in 16.6% vs 14.0%.

The crude percentage of cirrhotic patients 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 [Odds Ratio (OR) = 10.09; Confidence Interval (C.I.) = 7.63, 13.43]. Other significant predictors were age, gender and BMI; for age and BMI, residual analysis confirmed a linear effect. Notably, after adjustment for significant predictors, the likelihood of cirrhosis in the PITER cohort was reduced by about 40% as compared to the MASTER cohort (OR = 0.61; C.I.= 0.51, 0.72); in addition, being non-Italian was associated with an increased risk of cirrhosis (OR = 1.56; C.I. = 1.22, 1.99).

Non-Italian Natives

As expected, within each cohort, non-Italian patients were younger and showed a higher prevalence of females; positivity for HBeAg or anti-HDV was more frequent among immigrants; 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 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 analogues (NUCs) at the time of enrolment 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 an 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 >2,000 did not receive treatment; in the MASTER cohort the corresponding percentage was 62%.

DISCUSSION

The rapid evolution of the clinical and epidemiological burden of HBV infection in Italy is primarily due to three factors: 1. The ongoing effect of systematic anti-HBV vaccination; 2. The widespread use of antiviral drugs that block the progression of the liver disease and abolish the infectivity of patients and 3. immigration from areas where HBV is endemic.

The role of each factor and the modification of its weight over time appear clearly from the present study. As recalled in 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, as compared to 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 to 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 mono-infection. 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, beside the individual benefit discussed above, may acquire the value of treatment as prevention (TAsP) 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 TAsP has been thoroughly assessed for persons with HIV who achieve optimal viral suppression while under therapy [19]. Since young persons with HBV are predominantly of non-Italian origin, once again, programs to reduce the barriers to access to therapy are needed.

Co-infection with HDV was detected in 9.3% of study participants overall, with a higher prevalence among non-Italian natives. There was a positive trend as compared to the MASTER study towards testing HBsAg positive patients 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 HBV mono-infected patients for the reasons discussed above. 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, gender and BMI. Interestingly, the model showed that being part of the PITER cohort, other characteristics being equal, lowered the likelihood of cirrhosis by about 40%, as compared with the MASTER cohort. We can hypothesise that 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 confounders were controlled, non-Italian natives showed a high likelihood of cirrhosis; the prevalence of more aggressive HBV/HDV genotypes or sub-types, 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 present studies. In any case, the analysis suggests caution in interpreting crude prevalence in clinical/epidemiological studies.

Non-Italian natives account for 22%–27% of the patients in the present and in the MASTER cohort, respectively. Migrants were definitely younger than Italian patients in both cohorts but older in the present 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. Since enrolment 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, adherence to prophylaxis may be suboptimal among non-Italian women [28], so 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 resident 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 multicentre design allows a realistic view of the health status of the HBV patients who are somehow linked to care, it may suffer from potential heterogeneity of methods and evaluations; regardless, the strict connections of the centres 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 centres 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 centres participating in PITER was smaller, and each enrolled a higher number of patients than did the MASTER study; this could reflect the national policy in recent years of combining the regional centres 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 centres. A further limit of the present data was that more sophisticated 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 the HBV infection among Italian natives, and highlight new needs to meet health demands.

DECLARATION OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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FIGURE LEGEND

Figure 1

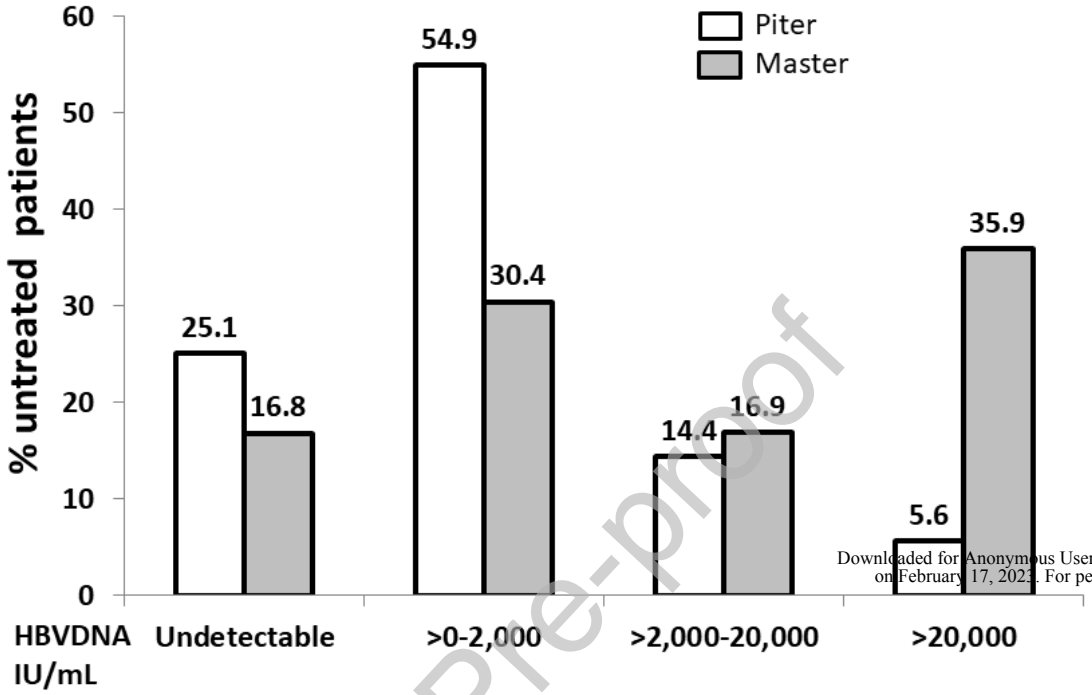

Figure 1. Distribution of untreated patients according to HBV DNA plasma concentrations

Table 1. Main characteristics of the patients at enrolment. Missing data were reported when >5%

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
Gender (Male)	2850 (62.27)	2003 (68.60)	<0.0001
BMI Missing 20.0%	24.14 (22.07-26.70)	23.83 (21.91-26.22)	0.0049
BMI ≥ 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
HBeAg Missing 5.2%	322 (7.17)	323 (12.31)	<0.0001
HBV-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-HDV Missing 29.1%	314 (9.28)	161 (8.31)	0.2329
Anti-HCV Missing 21,7%	169 (4.56)	81 (3.73)	0.1283
HCC	210 (4.64)	110 (3.80)	0.0827
Previous Therapy (mainly IFN based)	1354 (31.84)	983 (33.66)	0.1046
Ongoing therapy	3043 (66.56)	1000 (34.25)	<0.0001

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

Variables Median (Q1, Q3) or n (%)	**Piter Study** **Cirrhosis** n=1107 (24.15)	**Master Study** **Cirrhosis** n=722 (24.75)	***p*-value**
Age (Years)	63.63 (55.58, 71.89)	57.23 (47.68, 65.52)	<0.0001
Gender (Males)	816 (73.91)	577 (79.92)	0.0032
BMI	25.59 (23.18, 28.34)	25.59 (23.45, 27.92)	0.9063
BMI ≥ 30	127 (15.34)	92 (15.11)	0.9040
HBV-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 America 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
HBeAg (Positive)	54 (4.97)	81 (12.64)	<0.0001
Anti-HDV (Positive)	213 (24.80)	88 (17.50)	0.0017
Anti-HCV (Positive)	71 (7.85)	35 (6.06)	0.1900
HCC (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

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

	Odds Ratio	95% Confidence Interval	Wald $\chi 2$ statistic	*p*-value
Cohort (Piter vs Master)	0.61	(0.51, 0.72)	31.77	<0.0001
Gender (Females vs Males)	0.43	(0.35, 0.52)	77.27	<0.0001
Age (linear effect, x 5 year increment)	1.32	(1.27, 1.37)	210.43	<0.0001
BMI (linear effect, x unit increment)	1.03	(1.01, 1.05)	6.08	0.0137
Anti-HDV (Present vs Absent)	10.09	(7.63, 13.43)	256.58	<0.0001
HBeAg (Present vs Absent)	1.15	(0.83, 1.58)	0.75	0.3857
Anti-HCV (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

	Patients of non-Italian origin			Patients of Italian origin		
Variables Median (Q1, Q3) or n (%)	**Piter Study** n=953 (21.80)	**Master Study** 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*
Gender (Males)	496 (52.10)	453 (58.08)	*0.0129*	2223 (65.10)	1547 (72.43)	*<0.0001*
BMI	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*
BMI ≥ 30	67 (8.82)	43 (7.14)	*0.2605*	397 (14.24)	228 (12.56)	*0.1020*
HBV-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*
HBeAg	114 (12.23)	166 (23.48)	*<0.0001*	198 (5.91)	157 (8.21)	*0.0014*
Anti-HDV	94 (12.26)	59 (11.07)	*0.5139*	205 (7.96)	102 (7.27)	*0.4372*
Anti-HCV	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*
HCC	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*